METABOLIC DISTURBANCES AS AN ETIOLOGIC FACTOR IN CARCINOMA

THE INFLUENCE OF CHOLESTEROL METABOLISM AND OTHER FACTORS

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INTRODUCTION: GENERAL OUTLINE

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PART II.

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Introduction

The idea that metabolic disturbances may be the fundamental factor in the development of malignant growth is by no means new. It has been expressed, rejected, and forgotten, only to reappear in a new guise, from the earlier days in which neoplasms attracted the attention of those who studied the course of diseases and inquired into their causation.

This fact is not without certain consoling elements, if we consider that the same thing may be said about the conquest of the air by aviation. The conception that man might fly by mechanical means dates back as far as the legends of ancient Greece. Ovid,* in his Metamorphoses, tells how Daedalus flew from Crete to Sicily, but how his son Icarus, when attempting to fly at a greater height, perished because of the technical imperfections of his artificial wings. The progress of modern science, however, has converted the phantasies of classic mythology into concrete fact. The aeroplane not only proved to be a deciding factor in recent warfare, but promises to acquire an even greater importance in the commercial and industrial developments of peace.

In recent medical literature the metabolic and chemical features of pathologic conditions and physicochemical factors, such as ionization and the properties of colloids, are receiving more consideration than ever before. The invention of new apparatus capable of overcoming technical difficulties seems largely responsible for this trend in modern medicine. But the fact remains that such a tendency can be observed, that it has already made more effective the treatment of disease in general, and that this should stimulate our efforts along biochemic lines in cancer research.

The development of any given train of thought always offers points of interest when this development can be traced in history. I shall therefore

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* The Metamorphoses of Ovid, literally translated into English prose with copious notes and explanations by Henry T. Riley, B.A., of Clare Hall, Cambridge, London, Bell and Daldy, 1870, Book VIII, Fable III, 189-291.

attempt to outline the historical development of the conception of malignancy as a disease of metabolic origin. This outline will be chiefly concerned with the theories relative to the metabolic origin of carcinoma, although metabolic disturbances resulting in biochemic anomalies of a somewhat different character might also give rise to the development of tumors of a different type. A review of the historical development of the biochemic conception of cancer is given in Part I of this paper. Part II contains a summary of the considerations, data and personal observations which have led me to express the conviction "that physiologic chemistry will not only explain the causation of cancer, but eventually find its cure". In Part III recent personal data and observations are given to support the view that biochemistry will solve the cancer problem by enabling us to recognise and to rectify the functional inefficiency of internal organs which is responsible for the metabolic disturbances underlying and promoting lawless cell proliferation.

The objection might be raised that to believe in the metabolic origin of cancer is to revert to the ancient, much derided conception of humoral pathology; that it implies retrogression instead of progress. I do not believe that such is the case. It was not because Icarus attempted the unattainable that he perished when endeavoring to fly, but because the mechanical means at his command were inadequate. Thus the old humoral pathologists did not become the laughing-stock of modern medicine because the fundamental principle perceived by them was nonexistent, but because their knowledge and their equipment did not suffice to demonstrate what their mental vision saw.

The importance of the chemical composition of the body fluids, to use the antiquated term, is tacitly admitted by modern therapeutics: In the treatment of pernicious anemia transfusions supply to the patient the kind of blood which his own body is unable to manufacture. We know that as long as the foreign supply holds out the condition of the patient shows a marked improvement. The grouping of donors and recipients shows that the composition of the blood has to be taken into consideration. If an excess of the thyroid hormone in the blood in hyperthyroidism so far has not been demonstrated chemically, because of the minute amount present in the circulating blood, we know, nevertheless, that ingestion of the active principle of the thyroid (Kendall's thyroxin, a chemical compound) is capable of producing temporarily the symptoms of hyperthyroidism in a normal person as well as in a patient suffering from myxedema. Bacteriology, the most modern branch of medicine, has given us immunising serums whose curative powers are manifest though their chemical composition is not yet understood. But we do know that the diphtheria antitoxin and the serum used in poliomyelitis are products of the animal organisms.

Since the life of the body cells depends on their blood supply, the chemical composition of the blood cannot be immaterial; it must affect the welfare of the cells, their growth, and their rate of proliferation.

The microscope, although indispensible in cancer research, has only enabled us to recognize and classify the products of malignant disease: its use has given us no clue to the causative factors that underlie the lawless proliferation of cells.

In the fight against diabetes, a disease now admitted to be the result of metabolic disturbances, the microscope also proved to be an inadequate weapon: the use of the test tube enabled us to recognise the nature of these disturbances and the effect of our therapeutic measures.

If it be true that the chemical composition of the blood affects the proliferation of cells as vitally as does their blood supply, the chemical aspects of malignant growth must be of paramount importance, and we have a right to expect that the test tube will prove to be our most powerful weapon in the fight against malignant disease.

I hope to show, however, that far from minimising the magnificent work that has been done under the banner of cellular pathology, acceptance of the biochemic conception of malignant growth will help to verify and explain the observations of those who looked upon the cell unit as the key to the cancer problem.

The interpretation of the phenomena of malignancy will change when faulty metabolism is admitted to be the fundamental factor in the development of neoplasms. The cell unit will no longer bear the burden of the indictment: It will be considered the victim of untoward circumstances. But the fact will stand out that the patient labors of the pathologist were needed to bring us to the goal of cancer research - the defeat of malignant disease.

PART I

THE HISTORICAL DEVELOPMENT OF THE CONCEPTION OF CARCINOMA AS THE RESULT OF METABOLIC DISTURBANCES*

Chapter I

FOUR PERIODS IN THE DEVELOPMENT OF THE CONCEPTION

THE RELATION OF THE PERIODS TO EACH OTHER

A modern investigator who tries to inquire into the etiology of cancer might be perplexed by a choice between the two following considerations: Does the cell unit deserve the chief blame for malignant proliferation, because of its structural imperfection, or does the organism as a whole, since it provides the conditions that regulate the structural development of the cell?

No such dilemma existed for those who first observed and studied the occurrence of tumores praeter naturam. To them the cell unit was an unknown quantity. It is not surprising, therefore, that in their conception of malignancy they should have considered the organism in its entirety as the chief and initial instigator of malignant growth, and concluded that cancer was a constitutional rather than a local disease. It is remarkable that notwithstanding the progress achieved in every field of scientific research this primitive conception of malignant growth should have survived for more than twenty centuries. Many theories have been brought forward and supported by experimental evidence, each of which seemed capable of reducing ad absurdum the idea that metabolic disturbances could be responsible for the development of neoplasms. The idea itself has undergone many startling transformations, but the fundamental principle which it represents seems to possess a truly astounding vitality. This is significant.

* In compiling this historical review I have made extensive use of J. Wolff's Lehre von der Krebskrankheit. This work might be described as an encyclopedia on cancer research. It consists of three volumes of about 3000 pages, and gives data on all the theories as well as the experimental work connected with the study of malignant disease up to 1913. The book was brought to my notice by a reference in Hedinger's article, but, owing to the war, I only succeeded in obtaining a copy in July, 1917. This fact may be of interest in connection with the development of my own conception of the etiology of malignancy described in Part II.

The history of the conception of malignant growth as a disease of metabolic origin may be roughly divided into four periods which overlap. The division, even if somewhat arbitrary, has certain advantages. It shows the logical sequence in the evolution of thought and enables us to review in chronologic order the various phases of this evolution, as well as the men who were the principal champions of a given phase. The following classification has therefore been adopted:

Period I. The period of the atra bilis theories . . 400 B.C. to 1690 A.D.
Period II. The period of the lymph theories. . . . . 1600 A.D. to 1800 A.D.
Period III. The period of the blastema theories . . . 1800 A.D. to 1850 A.D.
Period IV. The period of the diathesis theories. . . 1800 A.D. to the present day.

An interesting relation exists between these periods. They seem links in a chain and each period is, as it were, the lineal descendant of its predecessor. Thus, at first the black bile, the atra bilis, supposed to be produced by the spleen, is looked on as the source of all ills, including malignant tumors (Period I). But the black bile proves to be an elusive and undemonstrable entity. As a natural result another body fluid, the lymph, becomes the center of interest. The composition of the lymph, its acidity, alkalinity, fermentation or coagulation is next held responsible for the growth of tumors (Period II). Then Harvey's discovery of the circulation and Hunter's observations on the coagulability of the blood reveal the fact that the lymph is but part of the blood, that is, the blood serum. The blame is shifted from the lymph to the blood fibrin. The blood clot now becomes the starting point of malignant growth, the "cancer-bud" and, as such, is designated "blastema" from blastos bud (Period III). Even Virchow accepts this explanation at first, after finding tumor-cell emboli in the iliac veins of six patients with carcinoma. Simultaneously, however, the development of chemistry as an exact science calls attention to the factors which might influence the coagulability of the blood and its composition in general, thus inaugurating Period IV. I have chosen the term "diathesis"* to characterise this period in order to associate by one word all the divers theories that attribute malignant growth to some kind of wrong chemistry in the body. In this acceptation diathesis may be looked upon as synonymous with faulty metabolism in a general sense regardless of the fact that very dissimilar metabolic disturbances have each in turn been anathematised as the cause of cancer.

It will be seen that the conception of malignant growth as a constitutional rather than a local disease not only survived but developed and expanded as time went on. If the constant recurrence of any given train of thought is any criterion of its intrinsic value, this fact alone seems worth considering.

BIBLIOGRAPHY

1. Hedinger, E.: Primärer Leberkrebs bei zwei Schwestern. Centralbl. f. allg. Path. u. path. Anat., 1915, xxvi, 385-387.

2. Wolff, J.: Die Lehre von der Krebskrankheit, von den ältesten Zeiten bis zur Gegenwart. Jena, Gustav Fischer, Bd. I, 1907; Bd. II, 1911; Bd. III, 1913.

* The term diathesis will be used in this general sense in this paper although I am aware that it is often applied exclusively to the work and theories of French investigators; diathese arthropathique, scrofuleuse, and so forth.

Chapter II

PERIOD I

THE PERIOD OF THE ATRA BILIS (400 B.C. to 1650 A.D.)

HIPPOCRATES, GALEN, BRUNO DA LUNGOBURGO, LANFRANCHI, RYFF, PARACELSUS, VAN FORREST, VAN HELMONT

The interest of this period does not lie merely in the conception of the black bile, but rather in the surprisingly modern deductions that were based on such a primitive and erroneous estimate of the etiology of malignant growth. It is as if the men of this period saw through a glass darkly, and apprehended things which science would take centuries to reveal and explain. The records of these pioneers of medicine give a wonderful insight into the workings of the human mind and of its capacity for grasping fundamental principles in defiance of material handicaps.

Hippocrates (460-375 B.C.). According to Hippocrates all sickness is due to wrong proportions in the mixture of the body fluids, blood, mucus, yellow bile, secreted by the liver, and black bile, produced by the spleen. He held the black bile responsible for the formation of tumors, inasmuch as "it is composed of extremely noxious and acrid constituents", and described the development of malignant growth as follows: "Ulceratus a maligniore et acriore materia, quae initio depascitur*. Non ulceratus a mitiore, quae tempore putrescit et tandem ulcerat". It is interesting to note that Hippocrates here mentions an initial reabsorption of the malignant agent, as this suggests observations on the spontaneous regression of tumors, which was categorically denied for a long time but has since been admitted as beyond dispute (Rohdenburg, 1918). It is interesting also that Hippocrates located the production of the "malignant" bile in the spleen, the largest lymphoid organ in the body. For modern research has shown that there is some intimate, if not fully understood, connection between the activity of the

*Since "depascitur" means literally "grazed off", its interpretation as "reabsorption" would seem permissible in this reference.

lymphoid tissues, the progress of malignant disease, and even the curative effects of radiotherapy (Millot and Mueller, Murphy and Taylor, Stevens).

Moreover, Hippocrates already had observed the effect of the menopause on the incidence of malignant growth. His conclusion that the prognosis is less discouraging if the disease is treated early, before the cessation of the monthly period, has not been corroborated by the operative results obtained in young women. But other factors may have to be considered in this connection, and it seems possible that when metabolic factors receive more attention our conclusions will be revised and will result in the vindication of the ancient scientist. At any rate, the effect of the menopause on tumor growth is now generally admitted (Prinzing's statistics). The influence of the menopause and of castration on the chemical composition of the blood (one of the body fluids) is already being made a subject of study (Part II).

Galen (131-203 A.D), physician by special appointment to the emperor Commodus, shared the current opinion concerning the noxious properties of the atra bilis, but he was the first to emphasize that the danger lay in the inspissation of the black bile: the thickened bile predisposed to tumor growth. Melancholia was the result of this thickening of the black bile, and melancholy women appeared to be particularly subject to cancer. A recent observation may be mentioned in this connection. It seems to bear witness to the keen power of observation of the ancient physician and to connect his primitive conceptions with the medical investigations of today.

It was observed during the recent epidemic of influenza that great mental depression was a symptom of the disease in many instances. It was also noticed that malignant conditions were notably aggravated by the patient's having had influenza; tumors that had seemed quiescent became active; recurrence appeared to be frequent in patients who had been doing well before they contracted the disease. At the same time the influenza seemed to have a marked effect on the blood cholesterol values, causing them to be unusually high (See Part II). This curious coincidence of symptoms of mental depression, high cholesterol values, and an increased tendency to malignant proliferation, all associated with the epidemic, is interesting if we take into consideration the increase of the blood cholesterol values that frequently occurs after the menopause, and the tendency to melancholia as well as to malignancy that has often been observed after cessation of the menses. The coincidence suggests that the study of the chemistry of the blood may provide many a missing link connecting seemingly disconnected symptoms, and reveal facts that were dimly apprehended by the master minds of the past, though misinterpreted through lack of actual knowledge.

Galen's treatment of cancer was based on internal medication as well as local applications. His suggestions about diet have many an echo in modern therapeutics; his injunctions concerning the use of purgatives recall the frequent reference to chronic constipation in the histories of cancer patients, and the elimination of cholesterol by the feces, after reduction to coprosterol (McNee, Manfredi). The diet which he prescribes is singularly like that recommended today (Williams, Ross, Bulkley). He forbids wine, vinegar, old cheese, "high" meat, pickled meat, goat's flesh, venison, hare, cabbage and walnuts.* He recommends barley water, vegetables, milk, young goat, veal, and fish "living near rocks", and allows light wines. The mild climate in which Galen lived may have had some

* In many friendly discussions with cancer patients I have made a point of inquiring what types of food agreed or disagreed with them. I always try to give to the conversation the character of a mere talk, so as to eliminate the idea of a visit to a doctor, for which patients seem to think that a special mental attitude is necessary.

Galen's reference to vinegar and walnuts surprised me not a little, as several patients who were not afflicted with carcinoma of the digestive tract had volunteered the information that vinegar and walnuts never agreed with them, although these items had not occurred to me and I had not asked any questions about them. I found that meat disagreed with a considerable number of patients, but that bacon always agreed with them, even when meat did not. I cannot account for this, but might add that these data were furnished by a number of patients who had never even heard of each other. Nor do the recent observations of Blunt and Mallon on the digestibility of bacon explain it, since they found that the bacon nitrogen was digested as well as that of other meat, while much or slightly cooked bacon gave an equal average (86.7 per cent) for the coefficient of digestibility of bacon fat, which does not differ from that for other soft fat. However, their observations were made on normal persons and not on cancer patients.

influence on the selection of foods which he recommended, but the effect of the diet on the blood cholesterol has been demonstrated eighteen centuries later (Rothschild, Luden). On the other hand, many of these dietary suggestions are the unmistakable product of the age in which he lived; his injunction that patients suffering from carcinoma "should drink the blood of geese" can scarcely be called modern.

During the following centuries the teachings of Galen became the foundation of all medical knowledge, but neither the Arabic physicians nor the clergy, who were the guardians of medicine in the Middle Ages, seem to have taken much interest in the etiology of malignant disease. A discussion of the various procedures by which tumors were treated would exceed the scope of this paper. It is enough to say that the use of arsenic paste and of the _ferrum candens_ (cautery), and attempts at surgery which were truly remarkable, when we consider the scanty anatomic knowledge of the time, constituted the sum total of the attention paid to neoplastic growth. Cancer was looked upon as an incurable disease, for which _noli me tangere_ was the safest precept, and the black bile was tacitly admitted to be the cause of its development. Hence the next reference to etiology of malignant growth does not occur until the middle of the thirteenth century, when Bruno da Lungoburgo (1252) called attention to the fact that "melancholy blood" was the cause of cancer, and should therefore be squeezed out with great care at operation. This is the first instance in which the composition of the blood itself is taken into consideration as connected with malignant growth, even if it must be admitted that "melancholy blood" is a somewhat vague and delightfully fantastic conception.

Lanfranchi (1250-1320), the founder of scientific surgery in France, who lived at Lyons after he had been banished from Milan, and was the author of the _Chirurgia parva_ (1290) and of the famous _Chirurgia magna_ (1296), also condemned the melancholy blood as the cause of malignancy. He advised the physician to bleed the patient white at operation. One cannot help picturing the smile on the face of the modern surgeon when reading these instructions, and remembering all the technical measures that are used today to prevent loss of blood in surgical procedures.

Paracelsus (1493-1541), (Philippus Aureolus Theophrastus Bombastus von Hohenheim), revolutionised the medical conceptions of his time. He was the first to question the significance of the black bile. He was also the first to surmise the effect of chemical agents in the formation of tumors. According to his theory the surplus of a mineral salt in the blood (the sal colcotharium) is the cause of neoplastic growth. The "rust" (product of oxidation?) of this mineral salt, which he calls sal calepino, is endeavoring to find an outlet when tumors ulcerate and break down. He states emphatically that the blood contains the causative agents which promote tumor growth: "Aus dem blut kommen alle offen schäden" (offen schäden was considered synonymous with malignant growth). But he recognised that injuries furnish an opportunity for the development of tumors and often determine their localisation: "Bricht aim etwas an der Leber, so leg es der Leber zu, bricht aim etwas am kopff, lege es dem kopffe zu". In the treatment of malignancy his efforts were directed chiefly toward rectifying the noxious composition of the blood, which he endeavered to improve by regulating the menses in women and by dietary measures. But the means he uses reveal his lack of chemical knowledge and are often pathetically funny: thus, "resin of gold"* and "gluten aequaticum", the latter from fish spawn, are recommended as "particularly effective" in checking the growth of tumors.

Still, one cannot help being impressed by the fact that Paracelsus, despite his many handicaps, intuitively recognised factors, the importance of which was to be conceded many centuries later. The effect of injury on the localization of tumors is no longer a matter of dispute with regard to sarcoma, even if opinions still differ as to the relation between trauma and carcinoma (Eunike, Faure, Sweit-

* The term resina auri is given by Wolff. It probably refers to the aurum potabile of the Arabic physicians, which Garrison says was considered a sovereign elixir against disease.

ser, Lazarus-Barlow, Williams, Ewing*).

Although the learning of Paracelsus did not include histology (all tumors were alike to him), and although his sal colcotharium and its "rust" may excite our hilarity, we are bound to admit that the fundamental idea, which connected the growth of tissues with the chemical composition of the blood, can hardly be called fantastic or altogether absurd in the light of our present knowledge. Garrison states that the writings of Paracelsus can be interpreted correctly only in the light of modern research. A greater tribute could not be paid to the genius of the ancient scientist.

The prestige of the atra bilis had been shaken by the caustic and witty criticisms of Paracelsus, but the teachings of Galen, nevertheless, retained their influence upon medicine until the middle of the eighteenth century.

Meanwhile the progress of anatomy had proved that the black bile was a product not of the spleen but merely of the imagination (Vesalius, Leonardo da Vinci). The blood on the contrary appeared to be omnipresent. Numerous wars and a closer study of the wounds they entailed had also called attention to the inflammatory reaction which accompanied the process of healing (Ambroise Paré, 1510-1590). It is not surprising, therefore, that the inflammation connected with malignant growth should have been taken into consideration and been attributed (by no means unjustly, as we know now) to the action of the blood.

Pieter van Foreest (1522-1597), whose title, the Hippocrates of

* Ewing states: "Mechanical trauma is an important factor in the causation of tumors. . . The figures represent the present attitude of clinical writers, which, as Lubarsch and Schimmelbusch have said, is often extremely uncritical. . . The frequency of the traumatic origin of tumors varies with different statisticians, according to their conception of trauma and their critical standard".

I might add that there is another factor well calculated to mislead the statistician, namely, the patient's conception of what constitutes an injury. I have a record of twelve cases at least in which no history of injury was specified by the clinician. An unofficial conversation with these patients revealed that they had suffered injuries which had a direct bearing on their condition, but had either "forgotten all about that", or decided that "everybody got hurt once in a while, and that they were not going to bother the doctor with such silly details", and this notwithstanding the fact that the clinician had made special efforts to obtain information with regard to former injuries.

Holland, denotes the esteem in which he was held by his contemporaries, concluded that tumores praeter naturam are the product of inflammatory processes in the blood. Walter Ryff, on the other hand, who was special physician to the City of Mainz, taught that the thickening of the blood due to menstrual disturbances or to chills caused the development of tumors.

The study of chemistry, although it was still at the chrysalis stage and had all the earmarks of alchemy, with the tendency to abstruse and fantastic metaphysical speculations which characterizes the Renaissance, resulted in the production of a host of far-fetched theories concerning the etiology of disease (The Academy of Medicine of Emperor Rudolph II of Germany, Libavius, Hieronymo, Cardano).

Jean Baptise Van Helmont (1577-1644), a Belgian friar who had studied medicine, introduced a new system of medical philosophy*, known as the Iatrochemical school, which is a typical product of the time. Having observed the production of a gas (CO^2) during the fermentation of wine (he called it "gas sylvester" and mistakenly considered it identical with the fumes of burning charcoal, CO), Van Helmont came to the conclusion that all life depends on the production of various types of gas as the result of chemical reactions. His interpretation of the physiologic phenomena is such as might be expected to occur to an ecclesiastic whose mind had been trained to look for the interference of spiritual agencies. He believed that the Archeus, a sort of sprite located in the stomach or in the spleen, controlled and directed the manufacture of the various types of gas upon which life depends. The ministrations of Archeus were, however, easily disturbed; psychic emotions, such as fright, anger, and mental excitement or worry, were apt to make Archeus furiosus and caused him to send his ferments into the wrong channels with the result that sickness developed. According to Van Helmont malignant tumors were a direct result of the wrath of Archeus: they did not occur

* Garrison attributes this philosophy to Paracelsus, while Wolff states that it originated with Van Helmont. As I could not ascertain which of the two has the prior rights and as I have based this historical review on Wolff's Lehre von der Krebskrankheit, I have adopted the latter view.

Nisi furor ille Archeus adfuerit.

However humorous this explanation of malignant growth may seem, it unquestionably reveals the power of observation of the old physician and illustrated the fact that his mind saw (albeit in a distorted picture, since he saw through the medium of very imperfect knowledge) many of the basic principles that are slowly being recognised today.

The recent investigations of Cannon and Crile have proved the influence of psychic stimuli on the secretion of the adrenal; the far reaching influence of the adrenal hormone is already conceded by many; to Van Helmont the suprarenal gland was an unknown entity, but the relation between mental strain and malignant growth has been pointed out by Bulkley*, whose statement is the result of observations on cancer patients during forty years.

It may be argued that the influence of mental factors has been recognised in other diseases, that psychic shocks are known to affect the development of exophthalmic goiter, and that worry has been admitted to be a factor in the formation of gastric ulcer (Bier, Bergmann, Friedman, Rogers). But it has also been shown that gastric ulcer is the precursor of gastric cancer in the majority of cases (Wilson and MacCarty).

Since the secretion of adrenalin is markedly affected by psychic emotion, it seems possible that the adrenal gland may furnish the link connecting mental strain and malignant growth. The following considerations support this deduction. In man the adrenal medulla and the adrenal cortex are so inextricably associated that one cannot well imagine how stimulation of the former can fail to affect the latter. We know that the medulla responds to psychic stimuli by an increased production or outpouring of adrenalin into the blood. We also know that the cortex is composed chiefly of lipoids and that these are principally composed of cholesterol and cholesterol esters (McCallum, DaCosta).

*"The nerve strain of modern life seems to be an element of importance, both through disturbance of metabolism and by direct action on morbidly deranged cells."

Ewing[10] stated not long ago: "There appears to be something in the chemical or mechanical nature of the irritation of cholesterol which is peculiarly effective in producing proliferation of the epithelium". Moreover, much evidence has been obtained that the adrenal cortex stores and "handles" the cholesterol for the organism (Rothschild, Sternberg, Gardner and Lander, Stewart, Weltmann, Hueck, McMeans and others); the adrenal, therefore, probably deserves to be called the chief organ of cholesterol metabolism. Factors calculated to overwork or exhaust the functional capacity of the medulla will also exert a deleterious effect on the adrenal cortex, leading to a disturbance of cholesterol metabolism. That such a disturbance exists in carcinoma is to be inferred from the abnormal blood cholesterol values, to which I have called attention (Studies on cholesterol V, VI).

The clinical insight of Van Helmont, who associated emotional stress and malignant disease, may thus be vindicated by modern research, and his elusive Archeus find a tangible representative in the adrenal gland when the functions of the latter are understood fully.

BIBLIOGRAPHY

CHAPTER II. PERIOD I.

1. v.Bergmann, G.: Ulcus duodeni und vegetatives Nervensystem. Berl. klin. Wchnschr., 1913, l, 2374-2379.

2. Bier, A.: Ueber das Ulcus duodeni. Deutsch. med. Wchnschr., 1912, xxxviii, 788-792; 836-842.

3. Blunt, L. and Mallon, M.G.: Digestibility of bacon. Jour. Biol. Chem., 1919, xxxviii, 43-48.

4. Bulkley, L.D.: Cancer, its cause and treatment. New York, Hoeber, 1915-1917, 2 vols., 230 pp.; 282 pp.

5. Cannon, W.B.: The emergency function of the adrenal medulla in pain and the major emotions. Am. Jour. Physiol., 1914, xxxiii, 356-372.

Cannon, W.B. and De La Paz, D.: The stimulation of adrenal secretion by emotional excitement. Jour. Am. Med. Assn., 1911, lvi, 742.

6. Crile, G.W.: The origin and nature of the emotions. Philadelphia, Saunders, 1915, 240 pp.

7. Da Costa, J.C., Jr.: A hand-book of medical treatment. Sajous, C.E.De M. and Sajous, L.T.De M.: Diseases of the ductless glands. Philadelphia, F.A.Davis Co., 1919, 65-197.

8. Eunike, K.W.: Trauma und Carcinom. Deutsch. Ztschr. f. Chir., 1918, cxlvii, 271-276.

9. Ewing, J.: Neoplastic diseases. Philadelphia, Saunders, 1919, 1027 pp.

10. Ewing, J.: Quoted by Bulkley, pp 110-112.

11. Faure, J.L.: Tumeurs d'origine traumatique. Bull. et mem. Soc. de Chir. de Paris, 1918, xliv, 794-804.

12. Forbes-Ross, F.W.: Cancer. The problem of its genesis and treatment. London, Methuen and Co. Ltd., 1912, 261 pp.

13. Friedman, G.A.: The probable endocrine origin of peptic ulcer. Jour. Am. Med. Assn., 1918, lxxi, 1543-1548.

14. Galen: Quoted by Wolff, 1, p. 13.

15. Gardner, J.A. and Lander, P.E.: On the cholesterol content of the tissues of cats under various dietetic conditions and during inanition. Biochem. Jour., 1913, vii, 576-595.

16. Garrison, F.H.: History of medicine. Philadelphia, Saunders, 1917, 2nd ed., 121; 147; 195.

17. Hueck, W.: Die Bedeutung der Nebennieren für den Kohlenhydrat- und Cholesterinstoffwechsel und über die Beziehung des Cholesterins zum Fettstoffwechsel. Centralbl. f. allg. Path. u. path. Anat., 1914, xxv, 397.

18. Lazarus-Barlow, W.S.: Malignant disease after injury. Brit. Med. Jour., 1918, i, 371.

19. Luden, G.: Observations on cholesterin retention as a factor in cell-proliferation. Jour. Lab. and Clin. Med., 1915-1916, i, 662-676.

20. Luden, G.: Studies on cholesterol. V. The blood cholesterol in malignant disease and the effect of radium on the blood cholesterol. Jour. Lab. and Clin. Med., 1918-1919, iv, 849-864.

VI. The value of blood cholesterol determinations and their place in cancer research. Jour. Lab. and Clin. Med., 1918-1919, iv, 719-735.

21. MacCallum, W.G.: A text book of pathology. Philadelphia, Saunders, 1918, 826-892.

22. McMeans, J.W.: Tissue reactions in experimental hypercholesterinemia. Jour. Med. Res., 1915-1916, xxxiii, 481-491.

23. McNee, J.W.: Cholesterin: an account of its relations to pathology and physiology. Quart. Jour. Med., 1913-1914, vii, 221-236.

24. Manfredi, L.: Sviluppo di alcuni germi in mezzi culturali addizionati di colesterina. Riforma med., 1917, xxxiii, 849-853. Abstr. Jour. Am. Med. Assn., 1917, lxix, 1479.

25. Millet, J.A.P. and Mueller, T.: Some phases of radium action with special reference to the hematopoietic system. Jour. Cancer Res., 1918, iii, 127-179.

26. Murphy, J.B. and Taylor, H.D.: The lymphocyte in natural and induced resistance to transplanted cancer. III. The effect of x-rays on artifically induced immunity. Jour. Exper. Med., 1918, xxxviii, 1-9.

27. Paracelsus: Quoted by Wolff, 1, p. 52.

28. Prinzing: Der Krebs in Württemberg und sein Auftreten in krebsarmen und krebsreichen Oberämtern. Ztschr. f. Krebsforsch., 1914, xiv, 412-490.

29. Rogers, J.: Fatigue disease as exemplified in functional disorders of the stomach and thyroid gland. Arch. Int. Med., 1919, xxiii, 498-510.

30. Rohdenburg, G.L.: Fluctuations in the growth energy of malignant tumors in man, with especial reference to spontaneous recession. Jour. Cancer Res., 1918, iii, 193-225.

31. Rothschild, M.A.: Zur Physiologie des Cholesterinstoffwechsels. III. Die Beziehungen der Nebenniere zum Cholesterinstoffwechsel. Beitr. z. path. Anat. u. z. allg. Path., 1915, lx, 39-65.

32. Rothschild, M.A. and Rosenthal, N.: The dietetic management of hypercholesterinemia in cases of cholelithiasis. Am. Jour. Med. Sc., 1916, clii, 394-403.

33. Sternberg, H.: Die Nebenniere bei physiologischer (Schwangerschaft-) und artifizieller Hypercholesterinämie. Beitr. z. path. Anat. u. z. allg. Path., 1915, lx, 91-123.

34. Stevens, R.H.: The blood in cancer under roentgenotherapy. Am. Jour. Roentgenol., 1917, iv, 215-216.

35. Stewart: Quoted by McMeans.

36. Sweitzer, S.E.: An analysis of forty-three cases of skin cancer. Jour. Am. Med. Assn., 1917, lxix, 179-182.

37. Weltmann, C.: Ueber das doppeltbrechende Lipoid der Nebenniere. Beitr. z. path. Anat. u. z. allg. Path., 1913, lvi, 278-324.

38. Williams, W.R.: The natural history of cancer. New York, Wm. Wood and Co., 1908, 519 pp.

39. Wilson, L.B. and MacCarty, W.C.: The pathological relationship of gastric ulcer and gastric carcinoma. Am. Jour. Med. Sc., 1909, cxxxviii, 846-862.

40. Wilson, L.B. and McDowell, I.E.: A further report of the pathologic evidence of the relationship of gastric ulcer and gastric carcinoma. Am. Jour. Med. Sc., 1914, cxlviii, 796-827.

41. Wolff, J.: Die Lehre von der Krebskrankheit, von den ältesten Zeiten bis zur Gegenwart. Jena, Gustav Fischer, Bd. i, 1907; Bd. ii, 1911; Bd. iii, 1913.

Chapter III

PERIOD II

THE PERIOD OF THE LYMPH THEORIES (1600 to 1800)

DESCARTES, LE DRAN, LOUIS, PEYRILHE, HUNTER, HOME, HEY, BURNS,

BROUSSAIS, LOBSTEIN, COOPER, VON WALTHER

Beyond revealing those flashes of genius that link ancient conceptions with modern research the period of the atra bilis had done little to further our knowledge of malignant disease. True, the blood had been taken into consideration as a factor in the development of neoplasms, but lack of chemical knowledge and technical facilities had prevented the influence of this factor from being verified. The crude observations that had been made resulted in speculations only.

The absence of positive findings in the blood, and the four great anatomic discoveries of the seventeenth century, the discovery of the chyle vessels by Aseli (1622), of the circulation by Harvey (1628), of the lymphatics by Olaeus (1652), and of the red corpuscles by Malpighi (1661)* - all naturally tended to focus attention, in this humoral era of medicine, on another "body fluid", the lymph.

The theories which connect the lymph with the etiology of malignant growth are in themselves a remarkable instance of evolution based on increasing knowledge. The first lymph theory (Descartes) looked upon the lymph as a liquid which merely "happened" to be in the body, but of which the chemical properties might be significant. The second lymph theory (Hunter) shows signs of progress inasmuch as its founder and his followers had come to realise that the lymph is an integral part of the blood (the modern blood serum) and inquired into the physical factors by which the lymph is altered. The third lymph theory (Lobstein) began to consider the physiologic activity of the lymph and even endowed it

* Malpighi used one of the first microscopes made by Zacharias Jansen, a Hollander. It is rather an interesting coincidence that the microscope should be a product of Holland, one of the smallest countries of Europe.

with "formative" properties, thus furnishing the link which connects this period with the next, the blastema period.

First lymph theory

René Descartes (1596-1650) and the Cartesian school of which he was the founder believed that malignant disease was caused solely by the physio-chemical properties of the lymph. The latter was in itself a more or less inactive substance. It merely obeyed physical laws and accumulated, either by obstruction or by extravasation. If it coagulated and hardened, a benign tumor (scirrhus) resulted. But if it happened to ferment, it acquired acrid and noxious properties and gave rise to malignant tumors. Hence the consistency and coagulability of the lymph, its fermentation, acidity and alkalinity, became the chief object of investigation. The Cartesian school directed all its energy to the elaboration of this conception of malignant disease. Its chief representatives were:

Le Dran (1685-1770), who was the son of a famous surgeon in Paris. His work is truly remarkable for the epoch in which he lived. He performed many necropsies and thus found cancers involving the stomach and the rectum. He distinguished four specific types of cancer: (1) cancer of the skin, comparatively harmless; (2) cancer of the breast; (3) cancer caused by the reflex of internal secretions ("cancer qui se forme par reflux des évacuations intérieures"); and (4) cancer produced by vitiated lymph ("produit par le vice de la lymphe"). The latter type was considered the most deadly of all. He held that a few drops of this vicious lymph might be arrested and retained by the lymph glands, but that if it failed to be thus held back and dispersed, it pervaded the body and caused the disintegration of all the lymph, and the patient was past praying for.

Antoine Louis (1723-1792) introduced new ideas concerning the properties of the lymph. He distinguished between gelatinous and albuminous lymph. The former was harmless and responsible for the development of goiters, but the latter produced malignant growth. His classification was based on the experiment of his friend Dufuoart, who had boiled a tumor and obtained a gelatinous mass.

Bernhard Peyrihle (1735-1804) believed in the theory of Descartes but modified its interpretation. According to him the origin of cancer was local. The lymph coagulated in a given spot and then became putrid through stagnation. Since only liquids were subject to putrefaction, there was no danger so long as a tumor was hard and dry, but as soon as it became "soft and damp" there was a general diffusion of poisons in the surrounding tissues, resulting in the diathese cancereuse. The lymph was rendered more easily coagulable by psychic emotions and luxurious living. It is interesting to note that although the lymph has long ceased to be considered a factor of etiologic importance the statistics of modern life insurance companies tend to corroborate Peyrihle's observations on the effect of high living on the incidence of cancer, and show that the disease is more prevalent among the rich than among the poor.

Peyrihle, moreover, was the first scientist who made use of animal experiments in his investigations. He injected carcinomatous material into a dog. Unfortunately the experiment was brought to a premature close by Peyrihle's housekeeper, who, worried by the dog's incessant howling, drowned the animal before any definite results had been obtained. In 1776 the highest award was made to Peyrihle by the University of Lyons for a thesis entitled Qu'est-ce que le cancer? In answering this question he found himself compelled to the conclusion: "Cette maladie est aussi defficile à définir qu'à guérir". Nevertheless, his inquiries into the nature and the etiology of cancer were conducted with so much insight and skill that his work, according to Wolff, will be of permanent value in cancer research.

Second lymph theory

"John Hunter (1728-1793), the founder of experimental and surgical pathology, . . . the pioneer of comparative physiology . . . One of the great all-round biologists, . . . and one of the three greatest surgeons of all time, whose work was as many-sided as his character" (Garrison), may be said to have exercised a twofold influence on cancer research. As a morphologist, pathologist, and surgeon he was instrumental in furthering the more accurate histologic study of neoplasms by focusing attention on the anatomic characteristics of the disease. His influence in this direction proved lasting and made him a fore-runner of cellular pathology. On the other hand his interest in physiologic problems caused him to evolve a personal interpretation of malignancy, revealing his genius, but so far ahead of his time that it found but little recognition among his contemporaries. He came to the conclusion that tumors were formed by activities of the organism in which they developed, that they were comparable to normal tissues, and that they lived and grew through being nourished by the body itself. A more modern conception of neoplasms can hardly be imagined.

His lymph theory was a strange compromise between his own insight and the teachings of his day. He recognized that the lymph is an integral, physiologic component of the blood, but at the same time he laid the greatest stress on the danger of the coagulation of the lymph, being convinced that coagulating lymph was the real starting point of malignant growth, even though tumors differed in appearance and structure. He therefore endeavored to prevent the extravasation of the lymph and its subsequent coagulation by compressing the blood-vessels in the immediate vicinity of the tumors. Neither his theory nor his therapeutic measures obtained a widespread popularity, and his adherents were chiefly English physicians, though his fame as a surgeon was unquestioned in the whole of Europe.

Everard Home (1756-1832), Hunter's brother-in-law (Garrison), who published his writings, but also "thievishly appropriated much of Hunter's valuable anatomic and pathologic collections" (Wolff), he even burnt part of the latter, was one of the followers of the Hunterian lymph theory. He deserves some credit, however, for making the earliest assiduous microscopic investigations of malignant tissues and for depicting in a beautifully illustrated publication what he considered to be "lymph granules", circular bodies which he had found in both lymph and tumors.

William Hey (1736-1819) and John Burns (1775-1850), pupils of Hunter's, directed their efforts towards establishing a clearer understanding of fungus hematodes and its relation to cancer. Hey's description of this type of tumor, "a mass which appears to have been formed by extravasated fluid (blood mixed with lymph) which subsequently became organised", is entirely in harmony with Hunter's theory.

It was, moreover, a direct result of Hunter's influence that a "Society for investigating the nature and cure of cancer" was formed, the first society ever founded for this purpose. This society's plan of investigation was modern in every respect. It aimed at settling some thirteen points, which are the object of research today; namely, the heredity, contagiosity, local or constitutional character of cancer, its relation to other diseases, the influence of climate and environment, the occurrence of cancer in animals, and other questions of minor importance. Unfortunately the aims of the association, like Hunter's conception of malignancy, were far beyond the comprehension of the times. Owing to lack of interest in the problems of malignant growth the society was dissolved in 1806, barely four years after it had been founded.

Reference should here be made to a French investigator whose views on the etiology of malignant growth represent a compromise between the English and the French lymph theories and whose influence on the progress of cancer research has been considerable.

Francois Joseph Victor Broussais (1772-1838), the "father of physiologic medicine", introduced the idea that inflammation is the etiologic factor in malignancy. According to him inflammatory conditions increase the local blood supply in the affected area. The lymph is a mere transudate from the blood, and its coagulation promotes tumor growth, because of the increased amount of nourishment which is deposited in one spot by the inflammatory process. The quantity of lymph decides the anatomic character of the tumor: the formation of hard (harmless) or soft (malignant) tumors depends entirely on the amount of lymph that has reached its destination. Inflammation, moreover, was always the result either of traumatism or of irritation. Hence, according to Broussais, the logical method of treatment could only be to remove the causes of irritation and the local surplus of blood supply.*

These views are by no means altogether absurd in the light of our present knowledge. Chronic irritation is known to promote malignant growth, even if "coagulating lymph" has been acquitted of any complicity in the matter. The beneficial effect of x-ray treatment has been attributed in part at least to the sclerosis of the blood vessels in areas exposed to radiation. The teachings of Broussais, or rather their interpretation by his contemporaries, among whom his influence was great, unfortunately led to that senseless bleeding of cancer patients known as "vampirism", which not only killed many victims but effectually hampered therapeutic progress for many decades.

Third lymph theory

Johann Frederick Daniel Lobstein (? - 1840), was the founder of the third lymph theory. His conception of malignant growth was as much an amplification of Broussais' teachings as the latter's views had been the result of a compromise between the Hunterian and the Cartesian theories. Lobstein himself was a pupil of Laennec's and one of those gifted, promising men whose talents come close to genius but whose careers are wrecked by self-indulgent folly. He held a professorship at the University of Strassburg, but combined the characteristics of a spendthrift and a profligate to such an extent that he succeeded in offending even the indulgent morals of his time and was obliged to leave the country. He died in poverty as a barber (Bandagist) in New York. He endeavored as a result of

* Broussais served as a surgeon in the Napoleonic campaigns; he was, as Garrison says "vieux soldat by training, and scolded and bullied with the vigor of Paracelsus"; which may explain his preference for Napoleonic measures and sanguinary methods.

Laennec's teachings to introduce the principle of tissue differentiation into his lymph theory, inasmuch as he distinguished between "euplastic" and "heteroplastic" lymph. By means of the former, normal or homoplastic tissues were formed, by the latter, all truly malignant tumors. The euplastic lymph became heteroplastic, or kakoplastic, through inflammation and the absorption of foreign substances ("substances étrangères à l'économie animale"). This changed, heteroplastic lymph developed into a "new molecule", which grew in a manner defying the laws of normal tissue growth, and thus became the starting point of cancer.

Wolff regards Lobstein's theory as "truly remarkable", and points out that if we substitute the epithelial cell for Lobstein's lymph molecule and divest his conception of some of its fantastic features, we must admit that we are confronted by the modern theories of Klebs and Ribbert.

Astley Cooper (1768-1841), one of Lobstein's warmest contemporary defenders, was a pupil of Hunter's and "the most popular surgeon in London during the first quarter of the nineteenth century" (Garrison). Cooper's busy life was so filled with his devoted care for his patients (he attributed his professional success to uniform and unfailing courtesy to rich and poor alike), his tireless study of anatomy through dissections, the improvement of surgical procedures, and the training of his pupils, that he had but little time to give to the problems of malignant growth. Nevertheless his endorsement of Lobstein's views made him a powerful champion of the third lymph theory, for his students adored him, followed his clinics in enthusiastic throngs and afterwards did much to propagate Lobstein's teachings.

Philip Franz von Walther (1786-1845), professor of pathologic anatomy at Breslau, was another prominent follower of Lobstein and, incidentally, a strong advocate of the constitutional origin of cancer. He defined cancer as "an ulcer of a specific type, which is both the result of, and a causative factor in a constitutional disease" ("welches mit einer konstitutionellen Krankheit in einem eigentümlichen Wechselverhältnis steht"). His principal aim in cancer research was to establish a rational classification of neoplasms. His chief contribution consists in careful and critical observations on tumors, with regard to both their anatomic localization and their histologic structure.

This tendency to devote attention to structural divergencies rather than to etiologic factors is the leading characteristic of the earlier portion of the nineteenth century. It must be looked upon as a necessary step in the progress of cancer research. A curious, faint, belated echo of the old lymph theories could be heard not long ago in a modern publication. In 1912 Gaertner of Pittsburg called attention to the "stagnant, nitrogenized lymph" which is found in malignant areas, acts as a stimulus on the cell nuclei and by means of which he claims to have produced cancer.

Lobstein's theory became the foundation on which, logically, a new conception of malignant growth was built up during the following period. His plastic lymph molecule developed into the "cell-bud" (blastema) of this new conception through the natural evolution of thought under the influence of more accurate methods of investigation.

BIBLIOGRAPHY

CHAPTER III. PERIOD II.

1. Aselli: Quoted by Wolff, i, p. 57.

2. Broussais, F.J.V.: Quoted by Garrison, pp. 415-418.

3. Broussais, F.J.V.: Quoted by Wolff, i, p. 97.

4. Burns, J.: Quoted by Wolff, i, p. 81.

5. Cooper, A.: Quoted by Garrison, pp. 419-501.

6. Cooper, A.: Quoted by Wolff, i, p. 87.

7. Descartes, R.: Quoted by Wolff, i, p. 57.

8. Gaertner, F.: Cancer. Its intracellular pathology caused by an autointoxicated lymph. Lancet-Clinic, 1912, cvii, 58-62.

9. Garrison, F.H.: History of medicine. Philadelphia, Saunders, 1917, 341-345.

10. Harvey: Quoted by Wolff, i, p. 57.

11. Hey, W.: Quoted by Wolff, i, p. 81.

12. Home, E.: Quoted by Wolff, i, p. 88.

13. Hunter, J.: Quoted by Wolff, i, p. 80.

14. Le Dran: Quoted by Wolff, i, pp. 59-60.

15. Louis, A.: Quoted by Wolff, i, p. 59.

16. Lobstein, J.F.D.: Quoted by Wolff, i, pp. 99-101.

17. Malpighi: Quoted by Wolff, i, p. 57.

18. Olaeus: Quoted by Wolff, i, p. 57.

19. Peyrihle, B.: Quoted by Wolff, i, 63; 64-66.

20. Von Walther, P.F.: Quoted by Wolff, i, p. 115.

21. Wolff, J.: Die Lehre con der Krebskrankheit, von den ältesten Zeiten bis zur Gegenwart. Jena, Gustav Fischer, Bd. i, 1907; Bd. ii, 1911; Bd. iii, 1913.

Chapter IV

PERIOD III

THE PERIOD OF THE BLASTEMA THEORY (1800-1850)

ANDRAL, BICHAT, CRUVEILHIER, LAENNEC, MÜLLER, LEBERT, BAYLE, CAYOL, RÉCAMIER, VOGEL

Just as the period of the lymph theories had been inaugurated by the discoveries of Harvey and Malpighi, Aselli, and Olaeus with regard to blood and lymph (discoveries that had been made possible by Jansen and Leeuwenhoek's very imperfect microscope), so the blastema period owes its birth to the discoveries of Schleiden, Brown, Raspail and Royer-Collard concerning the cellular structure of living tissues by means of Cruveilhier's superior achromatic microscope. Here again, the perfecting of technical facilities proved to be the starting point of a new era in the study of malignant disease.

Although brief, the blastema period must perhaps be looked upon as the most important period in the history of cancer research. The evolution of thought which it represents involuntarily calls to my mind the details of a scene which I observed long ago in Switzerland. Here a mountain stream that had been gradually increasing in volume divided suddenly into separate currents, which ran for a time in seemingly opposite directions. Under the influence of the geologic strata through which they passed, each branch of the small river assumed a color of its own. In the one the water was clear and transparent, revealing a thousand details of the river bed, in the other, the smaller and less important, it had an opaque though beautiful green-white color. But finally the two currents converged, after each had increased in volume by the addition of many small tributaries. They reunited, and the powerful river which they formed was characterized by the color of the smaller and less important stream. Similarly in cancer research the period of the blastema theory may be said to constitute the point of divergence of the clear and powerful river of cellular pathology and of the more turbid and apparently less important current representing the biochemic conception of the malignant growth.

Since it is my object in this paper to trace the historical development of the biochemic conception of malignant growth, a detailed account of the progress and achievements of cellular pathology cannot be attempted, but some of the main phases of its development and theories will be mentioned. Even in dealing with the growth of the metabolic conception of malignancy in Period IV little more than a bird's-eye view can be offered. The ever widening river of knowledge has been swolled by a thousand tributaries, and a comprehensive account would far exceed the scope of this publication. Nevertheless, if the tendency to convergence of the two currents of thought referred to and the far-reaching results to be expected from their ultimate reunion can be demonstrated, my object will have been attained.

Since the period of the blastema theory represents the divergence of two trends of opinion concerning malignant growth, the representatives of this period must be divided into two groups, although the almost diametrical views held by these two groups originated, strange to say, in a single head.

Gabriel Andral (1797-1876) may be called the father of the blastema theory, as well as of the diathesis theory. He was the successor of Broussais as professor of internal medicine at the University of Paris, and the first clinician to take an active interest in the problems of malignant growth, which till then had been left entirely to the surgeon.

Garrison describes Andral as "a clear, methodic, analytic spirit, who opposed all scholastic eccentricity and fanaticism; who was the first to urge the chemical analysis of the blood in morbid conditions and the first to believe that there are primary blood diseases". His conception of malignancy may be summarised as follows: Lesions of secretion, nutrition, circulation and enervation form the substratum by means of which the structural pathologic changes found in cancer are brought about. The immediate result of these "secretory lesions" is the formation of two kinds of material, one of which acquires "formative" properties, while the other cannot become "organised" (produits inorganisibles, pus for instance). The body treats both types of material as "foreign bodies", and endeavors to eliminate them by an inflammatory reaction, which results in the production of a scar of gangrene.

The most suitable substance for the formation of malignant growth is according to Andral, the fibrinous mass which coagulates in the blood vessels during inflammation and which, if not eliminated, has a particular tendency to "organise". He states emphatically, however,: "Le cancer n'est pas une altération à part. Cette expression (cancer), toute métaphorique, qui appartient à l'enfance de la science, comme celle d'inflammation, n'indique que la terminaison commune d'altérations très différentes les unes des autres". In other words, Andral's clear, analytic mind saw beyond the visible product of malignancy, and recognised the fundamental disturbances that made tumor formation possible. The elements of error in his conception are the inevitable result of the restricted knowledge of his day. But the keen mental vision to which his conception bears witness hardly seems to deserve the scathing comment of Wolff: "The study of malignancy has been handicapped and brought back to the level of previous centuries, where it threatened to be completely bogged, by the teachings of Broussais and his followers . . . and by the muddled and incongruous views of Andral, the enlightened clinician who thought and wrote so clearly on all other subjects".

Wolff looks upon cellular pathology as the alpha and omega of cancer research. But modern medicine, which is beginning to attach more importance to causative factors than to terminal results, may yet reverse Wolff's verdict on the great French clinician, and show that although cellular pathology was a necessary step in the study of malignant growth, Andral's genius recognised a fundamental principle when he attributed the development of neoplasms to an underlying disturbance of metabolic functions.

The chief followers of Andral must be discussed as two groups: Those who looked upon malignancy as a "local" disease, caused primarily by specific cells of structural deficiencies within the cell, and those who considered it to be a "constitutional" disease, resulting from anomalies in the body chemistry. The former were the forerunners of cellular pathology, the latter, by emphasising the importance of the chemical changes associated with malignant growth, paved the way for the diathesis theories of the next period.

The forerunners of cellular pathology

Marie Francois Xavier Bichat (1771-1802), "the creator of descriptive anatomy" (Garrison), revolutionised cancer research by introducing a classification of tissues. Hitherto tumors had, generally speaking, been looked upon as a mere accumulation of living material, more or less foreign in composition to the body itself and consisting of coagulated lymph or fibrin deposits, which were in no way connected with and still less were derived from the anatomic stratum in which they developed.

Bichat was the son of a physician, the favorite pupil and intimate friend of Dessault (a surgeon who became famous by the improvements which he introduced in the treatment of fractures and aneurisms), and he took part as an army surgeon in the campaigns of the French Revolution. His classification of tissues is crude and not even based on microscopic observations (he never used a microscope), but his work proved to be of inestimable value in the study of malignant growth nevertheless. He ascribed certain special properties to each of the tissues that he described and looked upon them as similar to the "elements" in chemistry, but endowed with propriétés vitales. As he believed in the "vitalism" of his day (an occult force which presided over all reactions in matter), he assumed that the vital properties of a given tissue might somehow be altered, and that the result of this alteration was malignant growth. He defined life itself as the sum of the forces which resist death (Garrison).

According to Bichat all tumor formation, even carcinoma, originated in the connective tissue (tissue cellulaire) a view that seems paradoxical for the man who first insisted on the classification of tissues: "On peut donc le tissu cellulaire concevoir comme formant la base commune de toutes ces excroissances . . . . De même toutes les tumeures sont cellulaires, c'est leur caractère commun". It need hardly be emphasized that this conception makes Bichat the first exponent of Ribbert's famous Bindegewebs-Theorie, which describes the initial proliferation of the connective tissue as the primary cause in the development of carcinoma, inasmuch as it disturbs the normal balance of growth energy in the tissues (Gewebsspannung). Bichat was, moreover, the first to describe the fragility of the blood vessels in malignant neoplasms, to distinguish between the stroma and the parenchyma as components of tumors, and to observe the lobular structure of carcinomas. These observations alone would entitle him to a place of honor in the history of cancer research.

Leon Jean Cruveilhier (1791-1874), pathologist and surgeon, was far ahead of his time in his conception of malignant growth, although his views are a curious mixture of the "local" and the "constitutional" interpretations of the disease. He looked upon cancer as a malignant degeneration of normal tissues; a definition that might be called truly modern, were it not that the term degeneration, introduced by Laennec, was used at that time in the sense of substitution. His statement, "La dégénération cancéreuse est une lésion organique de la plus mauvaise espèce, commune à tous les organes, identique dans tous, aussi générale que l'inflammation", must therefore be interpreted with special reservations. The chief etiologic factors in malignancy are, according to him, scrofulous and venereal infections. His deductions were based on the gross anatomic aspect of tumors, for he scorned the use of the microscope as much as Bichat.

Cruveilhier considered that phlebitis dominates all pathology

(Garrison) and consequently looked upon metastasis as "des embolies cancéreuses", due to inflammation of the capillary vessels. He did much, however, for the progress of cancer research by denying emphatically that coagulated blood could become organized and transformed into tumor cells: "Le sang extravasé ne s'organise jamais: il a perdu tous ses droits à la vitalité; il n'est qu'un corps étranger" (1849).

In his time and for many years Cruveilhier's chief contribution to the study of malignant growths was considered to be his discovery of the "lait cancéreux", cancer milk, the fluid that can be squeezed out of tumor tissue. He taught that, although the anatomic structure of neoplasms might furnish important evidence with regard to their malignancy, the presence of this cancer milk should be looked upon as conclusive proof. This doctrine put him into a somewhat embarrassing position a few years later when he was the first to recognise and to describe the malignant characteristics of "colloid cancer" and these tumors failed to yield any cancer milk whatsoever.

René Theophile Hyacinthe Laennec (1781-1826). Although the name of Laennec is associated in our minds chiefly with his studies on pulmonary tuberculosis (of which he himself became a victim at the age of forty-five years), with his invention of the stethoscope, and his description of chronic diffuse interstitial hepatitis, or Laennec's cirrhosis, his researches concerning neoplastic growth are not less important. Wolff calls Laennec the reformer of modern pathology and adds that "he was the first to introduce a really scientific classification of tumors, the first to give an accurate, if rough description of the growth of carcinomata and the first to point out that scirrhus is not merely a precancerous condition, but a well defined type of cancer".

Garrison described Laennec as "a slight, nervous, aquiline figure, of a generous, tolerant, unaffected nature and refined feelings, who was modest about his work and cared more for his proficiency on horseback than for his fame".

In character as well as in personality Laennec vividly reminds one of the gifted poet pathologist of our day, Eugene Albrecht, whose brilliant career was also cut short by tuberculosis and whose contributions to the study of malignant growth have made his name famous in cancer research.*

Like Bichat, Laennec served as a surgeon in the army of the French Revolution, and it was the deplorable lack of interest in malignant tumors not less than the total lack of knowledge concerning them which characterised even the ablest surgeons of his time that called his attention to the problems of malignancy. He began his investigations by making sections of tumor tissue by means of a razor, an absolutely new procedure; these were the first sections ever made in the study of malignant growth. But he studied his sections with the naked eye only and never attempted to use a microscope, an omission which might be explained by the thickness of the cuts and the still very imperfect instruments at his disposal.

As the result of his observations with this crude method, he distinguished between "homologic" and "heterologic" tumors. The former resembled normal tissues, while the latter had a structure of their own, to which he gave the name of "encephaloid" because of its resemblance to brain matter. The selection of the term "encephaloid" was unfortunate and led to much confusion; for Laennec included tubercles, melanotic tumors and fungus hematodes in this group and his fame caused the designation to be adopted, although French and English scientists were just beginning to pay attention to the peculiar characteristics of melanomas and fungus hematodes.

* This similarity even includes personal appearance; I was struck by the resemblance of Laennec's portrait (Garrison, p. 419), to Eugene Albrecht's younger brother, who was my chief at the Gynecologic Clinic in Munich. The two brothers resembled each other closely; I never met Eugene Albrecht, but his tragic death (he died suddenly of pulmonary hemorrhage on the eve of the inauguration of the Senker Institute for Pathology at Frankfurt, of which he supervised the building as director) was still looked upon as a personal loss by the entire staff of the Pathologic Institute in Munich when I worked there, and I was told countless instances of his brilliant intellect, the charm and kindliness of his personality, and his heroic efforts to carry on his work even when the disease had all but broken his strength.

Eugene Albrecht died in 1908; his work will be discussed in Chapter V in connection with Ehrlich's theory of atrypsia. He was not only a pathologist of note, but an accomplished musician, an eloquent speaker, master of twelve languages, a born poet, and a deep thinker; his poems were published after his death. Oberndorfer

Laennec's conception of the development of malignancy may be summarised as follows: He recognized three stages in the evolution of tumors. The first stage, _état de la crudité_, represents the accumulation in lobular form of "several types of pathologic substance, which are not encountered normally in the animal organism". During the second stage, _état cérébriforme_, the lobular mass assumes a brain-like consistency. The third stage, _état de ramollissement_, inaugurates the liquefaction of the brain-like material, which takes a brownish red tone, the various component parts of the tumor being _juxtaposées, ou infiltrées et pénétrées l'une dans l'autre_ and the disintegration of the mass starts in the center, where it forms a cup-like depression, (_dépression en forme de godet_). It will be admitted that this is an extremely vivid, if crude, picture of the growth and the degeneration of tumors. The term degeneration was, however, applied by Laennec to the first stage only of malignancy, as it denoted, according to him, merely the displacement and substitution of normal tissue by those pathologic substances to which he called attention.

Laennec's observations led him to conclude that cancer only occurred in "internal organs" and he included the mediastinum as well as the lungs and the liver among the latter. He studied the growths which he found with minute care, however, and even traced their proliferation into the blood vessels and into the thoracic duct. His influence on cancer research has been far reaching, for his classification and his conception of malignant growth were universally accepted until the middle of the nineteenth century.

Johannes Müller (1801-1858), whom Garrison refers to as "the greatest German physiologist of his time, and, like Haller and Hunter, one of the great all-round medical naturalists", was the first to give any practical consideration to the cellular structure of neoplasms. He may be said to have introduced the conception of the cell unit into the study of malignant growth.

At the end of the eighteenth century, Bichat had pointed out that

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refers to him as "a meteor of genius whose work will live".

a cellular structure is the common characteristic of all tumors, but his statement had received little attention. Even Laennec's genius had failed to perceive that the structural elements of which tumors were composed might be not less important than their gross anatomic features, and the microscope had not yet been used in cancer research.

In 1826, the year of Laennec's death, Raspail called attention for the first time to the fundamental similarity between the tissues of plants and animals in a discourse held before the Société d'histoire naturelle in Paris. A year later he made the bold statement: "Toutes les parties organisées se forment au dépens des vésicules élémentaires microscopiques". This statement makes Raspail the earliest exponent of the cell theory, which as Garrison says, "became one of the fundamental principles of modern science".

Although botanists took an active interest in the cellular structure of plant tissues, although Schleiden proved that plants developed from groups of cells (1831) and Robert Brown discovered the cell nucleus in his study of orchids (1833), although Carl Ernst von Baer demonstrated the embryologic cell differentiation and discovered the mammalian ovum (1828-1834) and Henle described the epithelial cells of the skin and the intestine,* while Schwann (a pupil of Müller's), found the striped muscle cell and the sheath of the axis cylinder in nerves and emphasized the similarity between structure and growths in plants and in animals, neither physicians, surgeons, nor pathologists seem to have taken the connection between the cell and malignant growth into account, until Johannes Müller published his monumental work, Ueber den feineren Bau und die Formen der krankhaften Geschwülste, and with the aid of the microscope and a magnification limited to only 500 diameters demonstrated the cellular structure of tumors.

While this important contribution to the study of malignant growth gives Müller a claim to the title of "father of cellular pathology", prior even to that of Virchow, his views on the etiology of malignancy assign to him a place

* Henle described the epithelial tubules of the kidney, which are named after him, many years later, 1862.

among the defenders of the constitutional origin of cancer. He considered that only those tumors which do not contain cartilage, fat, cysts, or fibers, which recur after excision and eventually kill their victims, should be diagnosed carcinoma. He believed in the fundamental uniformity of tumor growth (Einheitssystem der Geschwülste) and merely distinguished therefore between benign and malignant tumors. Wolff remarks that "this most ancient and unscientific classification and Müller's defence of the incontrovertible laws, effectually reduced cancer research to the standard of Galen's days".

In order to explain the development of malignant growth Müller endeavored to find "the primary cancer cell". According to him this cell was not derived from existing fibers, but constituted the true seed of cancer, the semen morbi, this fundamental element of malignancy multiplied by the spontaneous growth of new cell bodies (an opinion shared by Schwann and Schleiden with regard to other cells, for Remak only demonstrated cell division in 1852). It was the destructive intrusion of these cancer seedlings between the existing tissues which caused the distortion of the normal histologic picture by malignant growth (Germinations-Theorie). The specific cancer cell was destined not only to become a turning point in cancer research but to remain for many years the main object of investigation and the bone of contention between German and French investigators.

In Germany the general structure of tumors was considered the only safe criterion of malignancy at that time. Müller's countrymen showed little enthusiasm for his theory, although they had accepted his classification of tumors. Low power magnifications were used almost exclusively to demonstrate the histologic anomalies of tissue structure in neoplasms.

In 1847 Ludwig Wilhelm Bruch (1819-1884), professor of anatomy at Giessen, published an extensive monograph on the pathologic-anatomic aspect of tumors (Die Diagnose der bösartigen Geschwülste) in which he openly censured the teachings of Müller. He stated emphatically that "the cancer cell is a perfect cell from a morphologic point of view; its chief characteristic being merely that its differentiation has been arrested, which makes it useless for the formation of tissues and only fit to serve the purpose of cell multiplication". Virchow demonstrated in the same year that the so-called cancer cell may assume any shape as the result of mechanical factors and the pressure of the neighboring cells, and that cancers do not contain any elements which are foreign to the organism as a whole.

The German line of research led Bruch to recognise the embryonic character of malignant tissue; it was to lead Virchow to trace the development of epithelial growths to the epidermis or to the proliferation of the epithelial cells in glandular structure.

In France, however, the specific element of cancer found numerous and ardent defenders. High power magnifications were employed by preference in order to discover the cytologic peculiarities that would prove the specificity of the cancer cell. Among French scientists Velpeau alone had the courage to proclaim "La cellule cancéreuse n'est pas l'élément spécifique du cancer: la cellule dite cancéreuse n'est qu'un produit sécondaire au lieu d'etre l'élément sine qua non de la maladie, et il doit y avoir au dessous quelque élément plus intime dont la science aurait besoin pour préciser la nature du cancer". (To this statement Wolff ruefully adds: "Until this very day, that element remains undiscovered".) Nor were Velpeau's views based on theories only, for as early as 1830 he made use of the microscope for diagnostic purposes, and in many instances was able to produce clinical evidence of recurrent malignancy in cases in which benign growths had been diagnosed by others, whose verdict had been based on the absence of cancer cells.

Hermann Lebert (1813-1878), Velpeau's chief opponent and one of the ablest investigators of malignant growth at that time, was a typical representative of the blastema period. He was born at Breslau, originally his name had been Lewy, but he lived in Paris for a number of years and his studies on comparative anatomy in the French capital caused him to adopt the French line of investigation in cancer research. He was afterwards made professor of anatomy and histology in Breslau (1859).

Lebert's extensive contributions to cancer research resulted from the fact that he was not only a first class histologist but also an excellent clinician, whereas Müller had attached little importance to clinical observations. Laennec had given to the study of malignant growth the first scientific classification of tissues; Lebert was the first to introduce a classification of tissue elements. Laennec had already made sections of tumors, but he had studied them with the naked eye; Müller had used the microscope, but merely on fragments of tissue, in which the cells had been isolated more or less by pulling or squeezing them apart (Zupffpräparate). Lebert was the first to make use of microscopic sections.

Lebert not only studied his sections under the microscope, but he also made accurate measurements of the cells which they contained, and determined the average size of the cell body, its nucleus, and nucleoli. These observations caused him to become the principal champion of the "specific" cancer cell. He considered that "la forme applatie, la petites se du noyau, l'irrégularité anguleuse des contours, le volume", all combined, made it impossible to confound a cancer cell with any other kind of epithelial cell. Hence his embittered controversy with Virchow, when the latter defended the derivation of epithelial tumors from primary epithelial cells, and his scathing comment, "La doctrine des cellules primaires est une fantaisie de l'esprit allemand"*, for Lebert did not consider his specific cancer element to be an integral part of the body tissues, but more or less a foreign body.

* The fact that Lebert had changed his original name, Lewy, may perhaps help to account for the sarcastic note which runs through his disputes with German scientists; for in connection with the place of his birth, Breslau, it suggests a Hebraic descent, which was by no means an asset in Germany, but was viewed with much more tolerance in France. In 1851 Lebert admitted whole-heartedly, none the less, "Nous regardons sans hesiter M. Virchow, professeur à Wursburg, comme le premier anatomo-pathologiste actuel d'Allemagne".

With regard to the origin of the cancer cell Lebert's opinions have not been expressed very definitely. He assumes, rather vaguely, that the cancer cell is derived "somehow" from the blastema, the latter being a toxic exudate from the blood, which is carried along not by the connective tissue, but by "irradiation" through the lymphatics. The stroma of malignant tissues in which the cancer cells were embedded was also a derivative of the blastema; it was composed of fibrous material and saturated, like the cells, with the characteristic cancer milk, according to Lebert, whereas Müller does not appear to have attached any importance to the liquid content of malignant cells or tissues.

Although Lebert devoted his energies chiefly to the cellular aspect of tumors, his views on the etiologic factors concerned in their occurrence are those of the true humoral pathologist. His conception of cancer reveals the pessimistic resignation of the clinician with regard to a disease against which he is powerless. It must be given in his own words: "Le cancer est un vice humoral diathesique, inconnu dans sa nature, héréditaire et incurable. Le cancer récidive à peu pres constamment"; a concise but most depressing definition.

It would be impossible to discuss in detail the immense field Lebert covered in his study of malignant growth. His investigations include every type of neoplasm known in his day, and countless clinical observations for which he can claim the priority.

The following may suffice to give a bird's eye view of his work:

1. He was the first to study the different types of epidermal cancer, and to call attention to the metastatic character of many tumors of the central nervous system.

2. He proved the invasion of the bladder by rectal carcinoma by injecting colored water into the intestine.

3. He made use of biopsy microscopically to diagnose cancer of the cervix.

4. He traced the relation between peptic ulcer and gastric cancer.

5. He compiled statistics on the age incidence of cancer based on 6447 cases.

6. He differentiated cancer and chronic mastitis and bestowed upon the latter the very modern name of hypertrophie glandulaire.

7. He described two cases of cancer of the breast in males.

8. He studied the relation between cancer and tuberculosis and investigated the melanotic tumors of horses.

9. He was reluctantly compelled in the end to admit the malignant character of his "pseudo-cancer" (cancroid), which he had first classified as a benign tumor because it contained no specific cancer cells.

10. He was the first to point out that carcinoma is much more common among the rich than among the poor, an observation recently corroborated by the statistical studies of Frederick L. Hoffman.

Lebert's influence on cancer research may be gauged from the fact that Wolff's Lehre von der Krebskrankheit contains no less than 137 references to his investigations in connection with the most varied problems of malignant disease. It is of interest also that the cell-inclusions which he was the first to observe and to describe, and his suggestion concerning the contagiosity of cancer, were to form the basis of the numerous "parasitic" cancer theories, whereas his famous monograph, Traité pratique des maladies cancéreuses et des affections curables confondues avec le cancer (1851), makes him the greatest among the fore-runners of cellular pathology.

The fore-runners of the diathesis theories

Four of Andral's followers, Bayle, Cayol, Récamier, and Vogel, seem to be entitled to this special designation, as they emphasized the importance of the chemical aspects of the cancer problem, although their general conceptions of malignant growth made them typical representatives of the blastema period.

Gaspard Laurent Bayle (1774-1816), a native of sunny Provence, who graduated in Paris in 1801 was to show that the good-humored shrug which expresses the average Frenchman's opinion of "un Provenceau" so very eloquently occasionally represents a mistake in diagnosis. In 1803 he made his mark in pathology by his original description of the coarse character of the tubercle and its identity with the pulmonary, granular, and other varieties of tuberculosis (Garrison). His work Récherches sur la phtisie pulmonaire, formed the basis of Laennec's subsequent studies of the disease.

But if Bayle's work on tuberculosis was both important and original his investigation on malignant growth must be accepted as an even greater contribution to science.

It had become a highly commendable custom with the French Universities to publish at intervals a review of the progress that had been made in the study of malignant growth, the data being collected by the men best qualified for the purpose. Le Dran had been the author of such a report in 1757. Bayle and Jean Bruno Cayol, professor at the Hôpital de la Charité in Paris,* were requested to furnish a critical survey of "the present day knowledge of malignancy" in 1812. These investigations were published in the Dictionnaire des sciences médicales; the names of Bayle and Cayol thus became linked inseparably in the history of cancer research. Their joint work contains not only an enumeration of all the types of neoplasms that had been observed at the time, but a critical analysis of the claim to malignancy which had been attributed to many of these growths. It also included observations on the formation of tumors in organs, that had not yet been considered the seat of malignancy, and furnished a wealth of clinical and histologic data, which were the result of their own independent researches and bear witness to the thoroughness and the broad vision with which their inquiry had been conducted.

* Even Wolff gives no details about the history of Cayol, apart from those mentioned above, and Garrison does not refer to him at all.

Bayle and Cayol came to the conclusion that only a chemical substratum resulting from constitutional anomalies (une diathèse) could explain the problems of the development and the recurrence of malignancy, the metastasis, and the terminal cachexia, but this view did not prevent them from paying minute attention to the histologic structure of tumors. They were the first to distinguish between "diathesis" and "cachexia", terms which till then had been used indiscriminately to describe the progressive debility that accompanies malignant disease. Bayle and Cayol used the word cachexia in the sense in which it is employed today, while diathesis, according to them, represented the sum total of the chemical anomalies that make malignant growth possible. They admitted, however, that they were as yet unable to define what these anomalies (vices humorales) consisted in. Neither the theory of the atra bilis, nor the lymph theories had furnished any explanation; neither the black bile nor any kind of vitiated lymph could be called the true cause of cancer.

They found that a number of contributary causes played a prominent part in the development of malignancy; tuberculosis, syphilis, hemorrhoids, trauma, all chronic irritation, and alcoholism in gastric cancer. The pressure of the corsets worn at the time seemed to be a factor in the development of mammary carcinoma. The garments in question seem indeed admirably suited to produce lesions by pressure, if we are to judge by the specimens exhibited in the museums in Paris; they resemble implements of torture rather than feminine raiment.

Bayle and Cayol stated emphatically, however, that the incidental causes which they enumerated were incapable of producing malignant growth in the absence of the constitutional diathesis: "Il existe une disposition intérieure, qui suffit dans certains cas pour donner lieu au cancer, et sans laquelle toutes causes extérieures, soit locales, soit générales, ne peuvent jamais produire cette maladie". Modern science has fully corroborated the accuracy of Bayle and Cayol's observations with regard to the influence of contributory factors in the development of neoplasms. We need but recall the case of the football player, reported by Coley, in whom an accidental kick on the elbow during the game caused a benign tumor, a fibroma, to develop; excision of the tumor was followed by a recurrence in which the growth began to give some slight evidence of malignant tendencies; it was found, microscopically, to be a fibrosarcoma; a second recurrence proved to be a spindle-cell sarcoma; at the third recurrence the tumor was found to present all the characteristics of the small-cell sarcoma, and extensive metastasis of the latter type of growth was found at necropsy. But it is hard to understand why in modern research those internal factors of whose activity Coley's football player furnishes such unmistakable evidence and to which Bayle and Cayol called attention more than a hundred years ago, should not have received more consideration. If in but one unfortunate person an accidental kick leads to the development of a tumor (in a game in which every player is bound to be kicked many times) and if, with each recurrence, the tumor shows progressive malignancy, it would seem a foregone conclusion that conditions produced by the organism of the unlucky football player must have been responsible for the clinical facts reported by Coley. This is tacitly conceded by modern science. We cheerfully admit that predisposition plays a part in the occurrence of neoplasms. Yet the tremendous practical importance of definite knowledge concerning the physiologic basis of this predisposition does not yet seem to have been recognized. For in the twentieth century we are still satisfied with the blissfully vague conception of Bayle and Cayol's disposition intérieure, the nature of which we do not take much trouble to discover, and this, notwithstanding the fact that the progress of science has put into our hands means of investigation such as Bayle and Cayol did not conceive even in fancy. Is it not time for workers in cancer research to devote all their energies to an exact identification of these predisposing causes, which are admitted to play a part in the development of malignant growth?

The second part of Bayle and Cayol's report contains a discussion of the types of tumors which at the time were looked upon as malignant, but of which the clinical course seemed to establish the nonmalignant character. They were the first to distinguish between ulcerating carcinoma (cancer ulcéré) and the various forms of ulcers in which carcinomatous changes might be expected to occur (ulcéres cancéreux): the latter comprised tuberculous and syphilitic lesions. At that time a great variety of benign and malignant conditions of the testicles had been grouped together under the name of sarcocele. Bayle and Cayol were the first to prove the unscientific basis of this classification. They retained the term sarcocele, applying it only to truly malignant growths, carcinoma and sarcoma, and to teratoid tumors, but they demonstrated the nonmalignant character of the tuberculous, syphilitic and inflammatory tumors by means of histologic findings and clinical observations. They also proved that the "steatomata" of the liver were true carcinomas by their histologic structure, not merely composed of fat. In order to prove the latter point, they resorted to the simple but ingenious procedure of placing the tumor on a piece of blotting paper and heating it gently on a coal shovel (pelle à feu); as no grease-spot resulted, they concluded that the tumor could not contain any fat. They performed thousands of necropsies and thus discovered the existence of primary carcinoma of the pancreas and primary carcinoma of the liver. But they also pointed out that in the liver cancers are extremely rare, and that hepatic malignancy usually results from metastasis. Wolff states that their investigation of hepatic cancer is the first scientific treatise of its kind, inasmuch as they considered the clinical and the pathologic-anatomic aspects of the disease as well as the differential diagnosis, and must be looked upon as truly classical. Bayle and Cayol also recognized the relation between nephrolithiasis and cancer of the kidney, but came to the conclusion that clinically a differential diagnosis is impossible, although the result of pathologic processes can be identified at necropsy. They observed the spontaneous regression of tumors as the result of acute inflammation and called attention to the precancerous symptoms of cancer of the esophagus. They found that in Paris at that time gastric cancer was responsible for 25 per cent of all deaths from carcinoma.

Bayle and Cayol made important observations on the clinical aspects of cancer of the breast, admitted a local stage of the disease, during which the prognosis is not altogether hopeless (as Bayle and Cayol made no distinction between adenoma, fibroma, and cancer, their localized cancers of the breast were probably benign tumors), but they considered that as soon as "ces petites callosités, (qui) sont des squirrhes de la même nature que la tumeur du sein", made their appearance, the constitutional character of the disease could no longer be questioned; the case then defied all treatment. Clinically they called attention to the edema of the arm, which "can even lead to gangrene", as the result of involvement of the axillary glands in mammary carcinoma, and they described the parathesias, the hydrothorax and the "hectic" fever which may be observed during the terminal stages of the disease.

An illustration of the scientific thoroughness with which Bayle and Cayol conducted their investigations may be of interest. It concerns a therapeutic measure that was in vogue at the time.

In 1810 Gourlay had published results in treatment of malignancy which he claimed to have obtained in the island of Madeira by the use of an ancient remedy* namely, the ingestion of lizards. He stated that the treatment was efficacious only in tropical climates and that only one special kind of lizard should be used.

Bayle and Cayol immediately procured specimens of these reptiles and had them identified by the most famous zoologists of the day, Daubenton and Mauduyt. The latter pronounced the lizards to be <u>le lézard gris des murailles</u>, or the gray variety which lives on sunny walls in Spain, Sicily and some parts of Germany. Bayle and Cayol now proceeded to give the "remedy" a thorough trial. One

* The therapeutic value of lizards is mentioned by Pliny, who prescribed them to be eaten roasted for epilepsy, and recommended carbonized lizard mixed with honey for ophthalmia.

of their unfortunate patients partook of no less than 400 lizards. The animals had to be swallowed alive, but even this drastic therapy did not seem to affect the cancer from which the patient was suffering. They rightly concluded, therefore, that the ingestion of live lizards should not be recommended as a cure for malignant disease.

It is interesting in this connection that the blood of lizards furnished the first biologic reaction that was ever made. Baldini, whose experiments are reported by Römer (1788), added it to coagulated human blood and found to his surprise that the coagulum dissolved. He then tried the effect of lizards on himself, and made careful observations on his temperature and heart action. An hour after ingestion of the reptiles - heads and tails were cut off, the skin removed, and the animal cut into pieces which had to be devoured while they were "still squirming" - he obtained a rise in temperature (he used a thermometer) and a marked increase in pulse rate, followed by nausea and diarrhea. The latter symptoms are scarcely to be wondered at; they may have been something in the nature of a reaction to foreign protein, but they assume a special significance in connection with recent investigations.* In 1903 Flexner and Noguchi called attention to the proteases and lipases in animal toxins, and especially in cobra venom. In 1909 Pearce demonstrated the endotheliolytic properties of these toxins, while Kyes showed that they give a chemical reaction with the lecithin and the cholesterol of the blood. In 1912 a substance with digitalis-like properties was found to be contained in the skin of toads by Boehringer, who called it bufonin and gave it the chemical formula $C_{19}H_{26}O_4$. About the same time a similar substance was isolated by chemical means from the skin of lizards. These observations reveal an interaction between the zootoxins and the blood lipoids, which may yet furnish the link between the ancient lizard therapy and modern cancer research.

Joseph Claude Anthelm Recamier (1774-1856), an eminent surgeon as

* Baldini's work is described in detail by Johann Jacob Römer in his dissertation on the therapeutic value of lizards "Ueber den Nutzen und Gebrauch der Eidechsen in Krebschäden, der Lustseuche und verschieden Hautkrankheiten", Leipzig, 1788.

well as an able pathologist, performed one of the first vaginal hysterectomies in uterine cancer. He was probably the man who at that time had the deepest insight into, and the most understanding conception of the problems of malignant growth. Like many of his contemporaries he assumed a local and a constitutional diathesis in cancer, without stating very clearly what this diathesis was supposed to consist in. But he combatted the teachings of Andral and denied that coagulated blood or fibrin could become the starting point of cancer. The findings which had led to this conception were, according to Récamier, merely evidence of a carcinomatous degeneration of the vein walls, or the result of invasion of the blood vessel by the tumor.

Récamier distinguished between "circumscript" and "diffuse" cancers. He believed that in the latter the normal tissues had "condensed" until they assumed a "solenoid" consistency (a term which he used because of the similarity of the tumor mass to the consistency of a potato), whereas circumscript cancers merely pushed the neighboring organs aside or, at the most, "infiltrated them". He states that this infiltration may also be almost imperceptible, so that the malignant process may be established long before we are able to detect its presence. Being an excellent observer, he also noticed that a different type of cancer appeared to be formed in the mucous membranes and in the epidermis. He was the first to use the term "metastases" for growths which were found at a considerable distance from the original tumor, and applied this term to the neoplasms which he found in the right ventricle in a case of primary carcinoma of the pancreas, and in the brain after mammary cancer. As a pathologist he put an end to the discussion concerning the nature of encephaloid and fungus growths by classifying them both as scirrhous cancer, a classification, which not only settled a dispute of long standing, but simplified matters considerably from a practical point of view for physicians and surgeons, since the scirrhous type was universally admitted to be malignant and as such worthy of operation.

As a physician Récamier called attention to several facts that were corroborated in later years by the investigations of men who commanded a far better equipment than he ever possessed. Thus, he observed that local compression, by diminishing the blood supply, could transform an inoperable into an operable tumor. He noticed the reduced coagulation in the blood of patients suffering from carcinoma. He was the first to point out that supernumerary organs, such as warts, and the "accidental" tissues such as scars, are apt, especially if exposed to chronic irritation, to be the starting point of cancer in older persons. He warned against the use of leeches, (that panacea for all evil in his day) in cases of malignancy, because he had observed that carcinomatous nodules were prone to develop in places where the leech had been allowed to bite. He was also the first to recognize that the "black vomit" in gastric cancer is not a special product of the disease, as it was considered to be, but that it is caused by hemorrhages and consists merely of chemically altered blood.

Récamier admitted the influence of heredity in malignant growth, which Bayle and Cayol had emphatically denied, and defended his views on this point by recalling the well-known likeness to ancestors, which proves that there are definite types of individuals. Here again we find that modern investigations are beginning to furnish evidence in support of conceptions which have long been branded as visionary and unscientific, for Keith has recently suggested that the differentiation of mankind into racial types may prove explicable through the predominant activity of one or another of the endocrine glands, and that this predominance itself may be the result of climatic influences. The hereditary transmission of racial characteristics is a well-known fact. Slye, moreover, has demonstrated by her experimental work with mice that the tendency to neoplastic growth can be transmitted by heredity.

As the logical result of his belief in the constitutional origin of cancer, Récamier attached much importance to dietetic measures in the treatment of malignant disease. He revived the interest in the therapeutic value of hemlock (conium maculatum), but concluded that the results obtained with the extract of this plant were probably due to the strict diet and the reduction of the amount of food, rather than to the medicinal (and toxic) properties of the drug. The use of hemlock in malignant disease had been reintroduced about the middle of the eighteenth century by Anton Freiherr von Störck, president of the medical faculty of Vienna and physician of the Empress Maria Theresa. It had been prescribed in ancient times as a remedy against many different diseases and enjoyed great popularity during the Middle Ages, but its use had been abandoned to a great extent even after the excitement which Störck's discovery had caused, and which Wolff compares with the "delirium of enthusiasm" created by the premature and accidental publication of Koch's experiments with tuberculin. Récamier claims, however, that he succeeded even in obtaining cures by the combination of hemlock and dietetic measures. If the assumption that malignant growth is the result of inadequate and reduced metabolism is proved to be correct, the marked increase of the metabolic rate (shown by profuse perspiration and severe diarrhea) which the drug produces may to a certain extent help to explain the beneficial effects of the hemlock, or cicuta therapy, as it was called. Recent investigations have shown that an increase of the metabolic rate is accompanied by changes in the chemical composition of the blood. (The cholesterol content of the blood was found to be inversely proportional to the rate of basal metabolism during the administration of the thyroid hormone in myxedema.) The great value of restricting the food intake in combination with small but frequent doses of roentgen rays has been pointed out by Cook in his new technique in the treatment of cancer.

Récamier's insight into the nature of malignant disease might be illustrated by many other quotations from his Récherches sur le traitement du cancer par la compression et sur l'histoire générale de la même maladie, a classic monograph, published in 1829, and the greatest contribution to cancer research from an analytic and therapeutic point of view. I might add, however, that Récamier called attention to the curative effect of erysipelas infections in malignancy, an effect on which the Coley treatment was to be based many years later, and that his famous warning to his contemporaries never to base the diagnosis of cancer on one symptom only, proved of inestimable value to cancer patients at a time when the cancer cell alone was considered to furnish all the evidence that was needed.

Julius Vogel (1814-1880). Whereas Bayle and Cayol's histologic and anatomic researches and Récamier's clinical and therapeutic observations had paved the way indirectly for the diathesis theories of the next period, the work of Vogel did so directly, because of the special attention which he gave to the biologic and chemical aspects of malignant disease.

Vogel, professor of pathologic anatomy at Halle, wrote one of the first German textbooks on pathology, Die pathologischie Anatomie des menschlichen Körpers (1845), in which he attacked the conception of the specific cancer cell with merciless logic. He stated that it is impossible to decide by the morphology of the single cell under the microscope whether such a cell represents a form of normal or of malignant growth, since in cancer various types of cells are always to be found representing the different stages of development of the cell unit. According to Vogel it was still more unreasonable to assume that the so-called cancer cell should behave like a foreign intruder, invading the body from without and in defiance of an intact epidermis. He therefore attributed malignant growth to the production of a hyperemic exudate, the latter being the result of constitutional anomalies (Krebsdisposition) which furnished the elements from which the tumor was built up. This conception of malignancy might be called a personal interpretation or perhaps merely a travesty of Andral's blastema theory.

Vogel, however, was too good a scientist to be satisfied with this purely theoretic explanation of malignancy. He directed all his efforts toward finding concrete evidence and a biologic basis for his assumption. He began by making systematic analyses of the inflammatory exudates and of the detritus which he found in the vicinity of tumors. He observed that the latter was composed chiefly of a tough, coarse, amorphous substance, resembling fibrin, which could be made transparent or dissolved by the addition of acetic acid, ammonia and caustic alkali, but that it also contained varying quantities of granules consisting of modified protein and fat. Vogel considered that neither the inflammatory exudate nor the coarse amorphous substance represented a specific cancerous substance, but that both were to be looked upon merely as the material from which, through biologic processes, cells and fibers could be evolved. He stated that apart from a general blastema, which served the purpose of nourishing the entire organisms, specific blastemas were furnished by the body and that the latter developed into specific tissues. Consequently he assumed that there were as many types of blastemas as there were types of tissues in the body.

In malignancy a superabundance of this normal formative material was produced as the result of chronic irritation or inflammatory and suppurative conditions, but here the site at which the blastema was deposited decided the nature of the tissue that was to be evolved from it. Thus the vicinity of bone tissue caused the amorphous material to be transformed into bone, while the vicinity of nerves led to the production of nerve tumors. This conception of malignancy was known as Vogel's law of anology (das Vogelsche Analogiegesetz, 1847); it obtained a certain amount of popularity in Germany, but was rejected by the Vienna school of medicine, which admitted only one type of blastema, and it became the object of an embittered controversy. Even Führer, who had been the pupil and assistant of Langenbeck* and as such an enthusiastic defender of the specific cancer cell in 1852, transferred his allegiance and became an equally ardent supporter of Vogel's views, endeavoring to prove the existence of the different types of blastemas by means of chemical reactions. He believed that nitric acid constituted a specific reagent by which the chemical character of different blastemas could be demonstrated,

* Langenbeck was the second investigator who used animal experiments in cancer re-

and he distinguished between an albuminous, a chondroid, and a glutinous blastema. The first produced the true carcinomas; it assumed a blue tone, which changed to bright yellow in from six to twelve hours when mixed with nitric acid. The second was the starting point of fibrous tumors and showed a dirty brown reaction, which eventually also changed to yellow, while the third type gave no color reaction, but merely became pale and transparent when the reagent was added. Führer assumed that these different blastemas were produced by slight disturbances of the normal process of growth and that apparently insignificant outside stimuli suffice to initiate the evolution of each individual type.

Crude and inadequate as these methods of investigation undoubtedly were, erroneous as were the deductions which Vogel and Führer based upon them, they constitute, nevertheless, the first modern attempt at biochemic investigation in cancer research. We know now that "the bright yellow reaction" which Führer obtained in the end by the use of nitric acid was none other than the xanthoproteic reaction, given by all proteins, while the blue and dirty brown colors he describes may have been furnished by many different constituents of the tissues tested, including bile derivatives, lipoids, and many of the building stones of the protein molecule, to quote Abderhalden's simile for the amino acids. But it should not be forgotten that at the time when these observations were made the derivation of tumors from the body cells was still a matter of dispute, and that the protein character of the cells themselves was only just beginning to be recognized. Vogel and Führer's work was, therefore, the work of pioneers who apprehended what the technical means at their command prevented them from demonstrating; but their groping efforts opened new fields in the study of malignant growth, fields which were to be tilled during the period of the diathesis theories and from which the harvest may be gathered in our days by the combined efforts of many workers.

search with any success; (Peyrilhe's first attempt had been frustrated before its completion). He injected the fresh juice of a carcinomatous tumor into the femoral artery of a dog and as the juice contained live cells, he was able to demonstrate the presence of metastatic nodules in the dog's lungs; this experiment is the first tumor-grafting on record.

BIBLIOGRAPHY

CHAPTER IV. PERIOD III.

1. Abderhalden, E.: Synthese der Zellbausteine in Pflanze und Tier. Berlin, Springer, 1912.

2. Andral, G.: Quoted by Garrison, p. 347.

3. Andral, G.: Quoted by Wolff, i, 102; 103.

4. Baldini: Quoted by Wolff, iiib, 438.

5. Bayle, G.L.: Recherches sur la phtisie pulmonaire. Paris, Gabon, 1810, 439 pp.

6. Bayle, G.L.: Quoted by Garrison.

7. Bayle, G.L. and Cayol, J.B.: Quoted by Wolff, i, 94; ii, 469; 564; 645; 709; 861; 1013-1014; 1105-1106.

8. Bichat, M.F.X.: Quoted by Garrison.

9. Bichat, M.F.X.: Quoted by Wolff, i, 89; 370-381.

10. Boehringer, C.H.: Quoted by Wolff, iiib, 440.

11. Bruch, L.W.: Quoted by Wolff, i, 143-144.

12. Coley, W.D.: Sarcoma of the omentum. Discussion. Ann. Surg., 1910, lii, 401.

13. Cook, F.R.: A new technique in the treatment of cancer. Med. Rec., 1919, xcvi, 1042-1048.

14. Cruveilheir, L.J.: Quoted by Garrison.

15. Cruveilheir, L.J.: Quoted by Wolff, i, 107; 167.

16. Flexner, S. and Noguchi, H.: The constitution of snake venom and snake sera. Jour. Path. and Bacteriol., 1902-1903, viii, 379-410.

17. Führer: Quoted by Wolff, i, 168.

18. Fürth, O.V.: The problems of the physiological and pathological chemistry of metabolism. Transl. by A. J. Smith. Philadelphia, Lippincott, 1916, 682 pp.

19. Garrison, F.H.: An introduction to the history of medicine. Philadelphia, Saunders, 2nd ed., 1917, 905 pp. p. 469.

20. Gourlay, W.: Observations on the natural history, climate and diseases of Madeira during a period of eighteen years. London, Callow, 1811, 158 pp.

21. Henle: Quoted by Garrison, 473.

22. Hoffman, F.L.: The mortality from cancer in the western hemisphere. Jour. Cancer Res., 1916, i, 21-48.

23. Keith, A.: The differentiation of mankind into racial types. Lancet, 1919, ii, 553-556.

24. Kolmer, J.A.: A practical text-book of infection, immunity, and specific therapy. Philadelphia, Saunders, 1917, 121-122; 352.

25. Kyes, P.: Venom hemolysis. Jour. Inf. Dis., 1910, vii, 181-184.

26. Laennec, R.T.H.: Quoted by Garrison, 419.

27. Laennec, R.T.H.: Quoted by Wolff, i, 91-93.

28. Lebert, H.: Traité pratique des maladies cancéreuses et des affections curables confondues avec le cancer. Paris, Baillière, 1851.

29. Lebert, H.: Quoted by Wolff, i, 136; 149; 177; 522; ii, 105; 269; 315; 391; 623; 681; 928; 1178; iii, 51-85; iiia, 238.

30. Luden, G.: Studies on Cholesterol. V. The blood cholesterol in malignant disease and the effect of radium on the blood cholesterol. Jour. Lab. and Clin. Med., 1918-1919, iv, 849-864.

VI. The value of blood cholesterol determinations and their place in cancer research. Jour. Lab. and Clin. Med., 1918-1919, iv, 719-735.

31. Müller, J.: Quoted by Garrison, 465-466.

32. Müller, J.: Quoted by Wolff, i, 129; 133.

33. Oberndorfer: Eugene Albrecht. Münch. med. Wohnschr., 1908, lv, 1539-1542.

34. Pearce, R.M.: An experimental glomerular lesion caused by venom (Crotalus adamanteus). Jour. Exper. Med., 1909, xi, 532-540.

35. Pettibone, C.J.: An intermediate textbook of physiological chemistry. St. Louis, C. V. Mosby Co., 1917, 328 pp.

36. Pliny: Quoted by Wolff, iiib, 436.

37. Raspail: Quoted by Garrison, 469.

38. Raspail: Quoted by Wolff, 126.

39. Récamier, J.C.A.: Quoted by Wolff, i, 104-106; 361; 391-393; ii, 598; iiib, 185; 288; 407.

40. Schleiden: Quoted by Garrison, 469.

41. Schleiden: Quoted by Wolff, i, 125-127.

42. Slye, Maud: The inheritance behavior of infections common to mice. Studies in the incidence and inheritability of spontaneous tumors in mice. Jour. Cancer Res., 1917, ii, 213-238.

43. Störck, A.F., v.: An essay on the medicinal nature of hemlock. London, Nourse, 1760, 100 pp.

44. Velpeau: Quoted by Wolff.

45. Virchow: Quoted by Wolff, i, 143; 181.

46. Vogel, J.: Pathologische Anatomie des menschlichen Körpers. Leipzig, Voss, 1845, 491.

47. Vogel, J.: Quoted by Wolff, i, 142; 160; 162; 171.

48. Wolff, J.: Die Lehre von der Krebskrankheit, von den ältesten Zeiten bis zur Gegenwart. Jena, Gustav Fischer, Bd. i, 1907; Bd. ii, 1911; Bd. iii, 1913.

Chapter V

THE PERIOD OF THE DIATHESIS THEORIES

(1850 to the present day)

CHEMICAL FACTORS IN MALIGNANT GROWTH.

THE COMPOSITION OF THE BLOOD. THE INORGANIC SALTS. THE DIET. ENDOCRINE FUNCTION.

ROKITANSKY, ENGEL, BENEKE, EHRLICH, SPUDE, ROSS, VAUGHN, ROBIN, FREUND,

AND KAMINER, AND OTHERS

The evolution of the conception of malignant disease did not only keep pace with the general progress of science, as has been shown in the preceding chapters, but it was governed and controlled by the technical means at the command of those who studied the phenomena of neoplastic growth. The most promising phase of this evolution belongs to the period of the diathesis theories, the era in which we live.

The period of the Atra Bilis had furnished evidence that the human mind can perceive fundamental principles even without the aid of mechanical instruments. The progress achieved in the study of malignancy during the following periods had been made along the lines of demonstrable morphology, because surgery and anatomy had been the first sciences which possessed methods and instruments capable of revealing the gross anatomical structure of the body. The finer structure of tumors had only been considered after Chevalier's microscope had provided the means by which this aspect of malignant growth could be made visible. Cellular pathology, equipped with instruments by which its contentions could be demonstrated, has, therefore, dominated cancer research, not only during the blastema period but well nigh until the present day. The biochemic conception of malignancy, on the other hand, had found but a few defenders. Contentions, which cannot be crystallized into proof, usually fail to carry conviction. Consequently, the "secretory lesions" of Andral, the "constitutional anomalies" of Bayle and

Gayol and even the crude analyses of Vogel had been given scant attention. True, the genius of Hunter, though he possessed neither apochromatic lenses nor histologic methods, had realised that "tumors are comparable to normal tissues, formed by the activities of the organism in which they develop" and that "they live and grow through being nourished by the body itself": and the first part of Hunter's contention had been proved correct. But, at the end of the blastema period the latter part of his conception of malignant growth still belonged to the realm of speculation, because physics, chemistry, and physiology, the sciences capable of unravelling the mysteries of growth and nutrition were only slowly acquiring their instrumentarium. Biochemistry, the future ruler of medicine and of cancer research, had not yet been born. The road by which this ruler would march to victory was to be paved during the period of the diathesis theories.

Few things are more readily conceded and less fully realised than the part which mechanical devices have played in the progress of science. The "imponderables" of the eighteenth century, light, heat, sound, and electricity, were converted into measurable entities solely by means of technical instruments. The history of the nineteenth century has been called an epos of the triumphs of mind over matter, but a few illustrations will show that these triumphs were achieved only when the tools were available by which speculation could be transformed into evidence.

The undulatory theory of light was propounded by Hooke and Huygens in the middle of 1600, the undulatory character of the light waves was proved by Young in 1801 by means of "Mr. Coventry's exquisite micrometer". The spectroscope enabled Frauenhofer to dissect the sunlight and to recognise the solar spectrum at the beginning of the nineteenth century; it was the instrument by means of which Kirchhof and Bunsen proved that every element reveals its presence by a signature "that cannot be forged or duplicated" (Williams); it helped Zeeman to demonstrate that light is an electric phenomenon. The photographic plate makes it possible to obtain a permanent record of the manifestations of light.

Heat, radiant energy, was not measured quantitatively until the thermometer had been devised independently by Reaumur, Celsius, and Fahrenheit at the beginning of the eighteenth century. The radiometer of Crooks, perfected by Nichols and Hull in 1895, registers the "warmth" of a single candle at a distance of two miles; it has furnished evidence that radiant energy "may be expressed in terms of heat, light photographic effect, and even physical pressure" (Williams). Langley's bolometer makes it possible to recognize one hundred millionth part of a degree of warmth; it records the heat of the invisible portions of the spectrum; it measures the temperature on stars many millions of miles distant from the earth.

Sound waves had been "heard" since time immemorial; their velocity was calculated by Moll and Van Beek in 1823. The resonators made by Helmholtz, in 1840, demonstrated the character of the individual wave-length. Edison's phonograph not only reproduced sound waves, but made them visible, 1877. De Forest's audion, a magnified vacuum tube, the lineal descendent of our well-known electric light bulbs, helps sound waves to travel distances far beyond the scope of the ordinary long-distance telephone (1920); it is the means by which radio-telephonic conversations have been carried on between Honolulu and Washington, D.C., a distance exceeding 5,400 miles.

The electric current, of which the exact nature is still a mystery, was first produced and generated at will through the agency of Volta's pile (March 20, 1800). Edison's carbon filament transformed the current into light eighty years later. D'Arsonvale's galvanometer and Lord Kelvin's ampere balance made it possible to estimate the volume of the current and to direct its energy to accomplish the thousands of tasks which electricity performs today. Rutherford's electroscope enables the investigator to make tests, which are 500,000 times more delicate than the finest spectroscopic analysis: his spinthariscope combined with Crooke's fluorescent screen makes it possible to "count" radium atoms by observing the luminous splash produced when a single atom strikes the surface of the screen, just as the effect of a rifle bullet fired into the smooth surface of a lake at a distance of half a mile may be watched through a field glass.

Technical instruments, which thus revealed the nature of phenomena that had long been observed without being understood, have proved useful in fields of research seemingly unrelated to those for which they were devised; Volta's pile became the tool of the chemist; it enabled Young to isolate an unknown element, metallic potash, the paradoxical metal which floats on water and bursts into flames when coming in contact with that fire-quenching liquid. The polariscope, constructed for the study of light-waves, makes it possible to identify chemical substances of which the properties resemble each other so closely as to defy differentiation by the investigator although microorganisms recognize and select optical opposites without any assistance. (Penicillium glaucum, for instance, grow exclusively at the expense of the dextro-rotary compound, when introduced into a solution of racemic acid, until finally the solution becomes levo-rotatory.(Moore)). Without the galvanometer the electric nature of chemical reactions, such as oxidation, could not have been demonstrated.

The progress of medicine has been controlled to the same extent by technical facilities. The finer details of the heart action are revealed by the electrocardiograph, which alone enables the physician to recognize certain cardiac disturbances, such as auricular flutter. Tashiro's biometer has made it possible to detect the minute amounts of carbon dioxid which are produced when a nerve impulse travels along an isolated nerve and which cloud the water-like transparency of barium hydroxid by the precipitation of barium carbonate. Haldane's perfected calorimeter furnishes accurate information concerning the rate of basal metabolism; it enables the surgeon to gauge the risk of operative procedures in cases of hyperthyroidism. The colorimeter reveals the minute amounts of numerous chemical constituents in the blood: sugar, creatinin, and uric acid to name but a few. Rohrer and Adler's refractometer makes it possible to study the "albumin-globulin ratio" in the blood during the process of immunisation; it demonstrates the increase of the globulins which heralds the activation of a latent tuberculous process. Michaelis' and Walpole's hydrogen electrodes are needed for the determination of the hydrogen ion concentration of the blood by the gas-chain method: they reveal the increased alkalinity of the blood in diabetes and in carcinoma (Menton).

The variety, ingenuity, and perfection of the instruments of precision which Science possesses in the third decade of the twentieth century have not been equalled at any previous time. Cancer research equipped with such an instrumentarium may be expected to solve the problems of malignant growth and to convert into demonstrable evidence the main contentions of the diathesis theories, all of which attributed malignant disease to biochemic anomalies resulting from metabolic disturbances.

The diathesis theories

The diathesis theories may conveniently be classified under seven headings representing the factors to which special importance was attached by the exponents of these theories. This classification has the advantage of permitting a concise outline of the numerous and diverse metabolic disturbances to which the development of malignancy was attributed. It should not be taken for granted, however, that the men to whom the name of chief exponents of a certain theory applies, defended such a theory to the exclusion of any other. Nor should it be forgotten, that manifestations of malignancy which were looked on as "causes" at the beginning of the period of the diathesis theories, were recognised to be merely evidence of the progress of the disease within a few decades, when the progress of science and the construction of new instruments permitted closer and more analytic investigation. It is possible, therefore, that chemical anomalies, which are now considered to be the result of the malignant process, if not an integral part of it, may be found to represent a defensive reaction on the part of the organism; thus, the high alkalinity of the blood observed in patients suffering from carcinoma may prove to be comparable to the febrile reaction, which is now recognised to be an asset for the victims of bacterial invasion.

Classification of the diathesis theories

Theories concerning:	Chief exponents:
1. Unspecified, "constitutional", chemical or metabolic factors.	ROKITANSKY, ENGEL, BENEKE, BROCA, VERNEUIL, EHRLICH, Wagner, Paget, Woodhead, Powell, White
2. Specific cancer toxins.	SPUDE, - Blumenthal, Kullman, Girard, Roger
3. Enzyme activity	Blumenthal, Wolff, von Leyden, Abderhalden
4. Specific chemical factors.	ROSS, VAUGHN, ROBIN, FREUND AND KAMINER
(Sodium chlorid, potassium, nitrogen, sulfur, cholesterol)	Braithwaite, Scherk, Beebe; Forbes-Ross; Blumenthal, Vaughan; Green, Kahn; Beneke, Robertson, Luden
5. The influence of the diet	Williams, Bulkley, Hoffman
6. The chemistry of the blood	Beneke, Benedict, Menten, Rohdenburgh
7. Anomalies of endocrine function	Webb, Beaver, Lorand, Seely-Little

BIBLIOGRAPHY

1. Alder, A.: Die physiologischen Schwankungen des Mischungsverhältnisses von Albumin und Globulin im menschlichen Blutserum. Deutsch. Arch. f. klin. Med., 1918, cxxvi, 61-72.

2. Alder, A.: Anhaltspunkte für die Prognosenstellung der Lungentuberkulose aus refraktometrischen Serumuntersuchungen. Ztschr. f. Tuberk., 1919, xxxi, 10-17.

3. Editorial. Refractometry. Modern Med., 1920, ii, 484-486.

4. Menten, Maud L.: The alkalinity of the blood in malignancy and other pathological conditions; together with observations on the relation of alkalinity of the blood to barometric pressure. Jour. Cancer Res., 1917, ii, 179-211.

5. Moore, F.J.: Outlines of organic chemistry. New York, John Wiley and Sons, 1915.

6. Rohrer, F.D.: Die Bestimmung von Albumin und Globulin. Deutsch. Arch. f. klin. Med., 1916, cxxi, 221.

7. Tashiro, S.: A chemical sign of life (irritability). Chicago, Univ. Chicago Press, 1917, 151 pp.

8. Williams, H.S.: The story of nineteenth-century science. New York, Harper and Brothers, 1901.

9. Williams, H.S.: Miracles of science. New York, Harper and Brothers, 1913.

THEORIES CONCERNING UNSPECIFIED "CONSTITUTIONAL", CHEMICAL AND METABOLIC FACTORS

At the end of the blastema period investigators fully realized the importance of a conclusive answer to the question: Is malignant growth a local disturbance, or merely the local manifestation of a generalized disease condition?

Three features of malignancy, distant metastasis, recurrences following excision after many years in sites far removed from the original field of operation, and the simultaneous development of multiple, divers neoplasms, had not been explained satisfactorily by the now recognized cellular structure of tumors, or even by the theory of the specific cancer cell. This caused Rokitansky and Engel, the first modern exponents of the biochemic conception of malignant disease, to emphasize, in 1840, the importance of the "constitutional anomalies" to which Bayle and Cayol had called special attention in 1812.

Carl Rokitansky (1801-1878). Rokitansky, the great leader of the Viennese School of Pathologic Anatomy was forced to the conclusion that mere morphologic changes are insufficient to explain the causation of disease, by the mass of pathologic material which he investigated. According to Garrison he "made 30,000 postmortems during his life and had, annually, the disposal of from 1500 to 1800 cadavers". He was unassuming and genial, a graceful writer and the ablest descriptive pathologist of his time; his personality radiated the good-nature and wit of Vienna (Garrison).

Rokitansky's Bohemian descent had endowed him with that imaginative vision, which characterizes the Slav as well as the Celt, but which to Virchow's precise, unimaginative Teutonic mind appeared to be a fault rather than an asset in a scientist. Rokitansky was convinced that invisible chemical changes in the fluids (blood and lymph) by which the tissues are nourished and also in the tissues themselves produced the visible tissue changes; this conception forms the basis of his doctrine of "crases and stases". Virchow, on the other hand, emphasized the importance of cell morphology to the exclusion of almost any other factor: no wonder the Father of cellular pathology and the ardent defender of the blood dyscrasias failed to understand each other when it came to the etiology of malignant growth. Rokitansky's explanation of malignancy is a compromise between the blastema theory and his own views on the effect of chemical alterations. He considered that chemical changes in the albuminous content of the blood, especially an increase of the albumin often brought about by inflammation, led to the production of a fibrous mass which became the starting point of cancer. Although Virchow at this time (1842-1846) still endorsed the blastema theory, and even interpreted the tumor metastasis which he found in the iliac veins in six cases of carcinoma several years later according to this conception, he "mercilessly chaffed Rokitansky's doctrine of 'crases and stases' out of existence" (Garrison). Rokitansky himself admitted that it was difficult to harmonize his chemical hypothesis with many anatomic findings, but he considered it defendable in view of (1) the actual findings in the blood (clots and metastasis), (2) the production of exudates in malignancy, and (3) the manifest antagonism between diseases such as cancer and tuberculosis, which, suggests that, inasmuch as cancer and tuberculosis virtually excluded each other, the cancer dyscrasia must be fundamentally different from the chemical alterations preceding tuberculosis. Garrison's interpretation of Rokitansky's views which implies that "chemical states of substances were actually conceived of as susceptible to 'disease'", does not seem quite fair to the great Viennese pathologist; Rokitansky did not teach that chemical states of substances were subject to disease: his contention was merely that different chemical disturbances furthered the establishment and the progress of different types of disease.

Modern investigation, revealing the importance of chemical factors for the production of clinical manifestations has already partially vindicated Rokitansky's scientific vision. Cramer, in 1919, showed, for instance, that calcium salts are needed for the development of gas bacillus infections; mice injected with the gas-producing bacillus failed to contract the disease unless they had been sensitized by the addition of calcium salts; these experimental findings explained the frequency of gas bacillus infections in certain military sectors of the French fighting line, during the War and the scarcity of this complication in adjoining sectors; bacteriologic analysis had revealed that the gas bacillus was practically omnipresent in the soil of France; the abundance or the lack of calcium salts in the soil was thus proved to be responsible for the prevalence or the absence of the disease. Virchow's sarcastic and seemingly justified criticisms made Rokitansky himself doubt the scientific value of his hypothesis of the "blood dyscrasias"; lack of technical appliances and analytic methods made it impossible for him to demonstrate the importance of chemical factors in disease. His doctrine of "crases and stases" may be called a distorted picture of scientific truths; its descrepancies alone were visible to his contemporaries, but posterity is in a position to appreciate the scientific insight of the great Viennese teacher and to make allowances for the inadequate terms in which his conception was necessarily expressed.

<u>Joseph Engel</u> (1816-1899). The name of Engel is linked as closely as that of Rokitansky with the theories of the blood dyscrasias: the "cancer dyscrasia" is his conception, strictly speaking. He was professor at Zurich, at Prague, and at Vienna and his writings did much to spread the teachings of Rokitansky. He was the first to call attention to the stroma of tumors, which he looked on as pathognomonic of malignancy. His classification of the divers types of stroma and his definition of the dyscrasia which paves the way for cancer are characteristic of his time. He distinguished between a "compact fibrous", a "sieve-like" and a "net-like" stroma. He described the type of blood promoting neoplasia in the following terms, "Abnormal blood, high in albumen, venous in character, dark in color, lacking in consistency and in coagulability, which fails to redden when

exposed to the air and has a tendency to hypostasis". The formation of exudates, according to him, represents an endeavor on the part of the organism to reestablish its "normal crase", but the exudate is apt to produce the blastema, needed for the formation of cancer. The chemical analyses of Heller (1803-1871), who worked with the Viennese surgeon, Schuh, who found in the blood of patients suffering from carcinoma a three to five-fold increase of fibrin with diminution of the red corpuscles and of the total solids, seemed to support the doctrine of the "crases and stases". In the end Engel attributed malignant proliferation to the effects of a single substance to which he gave the name "Krebsin". If the scientific vision of Rokitansky compels admiration, the endeavors of his followers to furnish evidence in support of his conception cannot but strike one as pathetic; their efforts, praiseworthy though they were, not only failed to carry conviction, but often made the conception itself appear ridiculous; the undeveloped condition of chemistry and physiology constituted a handicap against which no efforts could be expected to prevail.

Friedrich Wilhelm Beneke. (1824-1882). Among German scientists Beneke, Professor at Marburg, was the principal champion of the constitutional etiology of cancer. As early as 1850, he had called attention to the abnormal proportions of the constituents of the "bone ashes" in carcinoma, to the early calcification of the rib cartilage and to the absence of oxaluria and phosphaturia in the first stages of the disease (Zur Physiologie und Pathologie des oxalsäuren und phosphorsäuren Kalkes). The contention of Stich, supported by Zenker (1875), that traumatism is directly responsible for the development of sarcoma, caused Beneke to attack the theory of the localized character of malignancy and to point out that traumatism alone is incapable of producing malignant growth, unless the conditions necessary for the development of neoplasms were furnished by the preëxisting constitutional tendencies found in so-called predisposed persons. Lack of normal proportions among the blood constituent is, according to Beneke, the basis of all constitutional anomalies; predisposition is a pathologic composition of the body fluids; the constant interaction between the body fluids and the tissues and organs makes the chemical composition of the body fluids of paramount importance, for it is inconceivable that an excess of albumin combined with an excess of hypophosphates, and a normal amount of albumin combined with an abnormally low percentage of hypophosphates should fail to produce different mixtures or different constitutions. The transplantation of tumors, (that is, grafts taken from human beings and transplanted into animals, a procedure used in experiments at that time) had proved unsuccessful; this Beneke looked on as evidence that the chemical conditions which prevailed in the body controlled the growth of tumors, and modern investigations concerning the fate of heteroplastic transplants have proved his surmise correct. The dyscrasia which predisposes to cancer is characterised according to him by the lack of oxidation of albuminates, phosphorous and iron, resulting in an excess of unoxidized albuminates and an increased amount of "cholesterin" and myelin in the blood. Beneke is the first investigator who has given a thought to the lipoids, especially the cholesterol content of the blood in malignant disease. His method for demonstrating the excess of myelin neoplasms is pathetically primitive; it consisted in adding sulfuric acid to thin sections of the tumor. The lack of oxidation in cancer which he suspected is, however, supported by the recent investigations of R. H. Greene, Rohdenburg and Vaughan: Greene demonstrated an increase of unoxidised sulfur, Rohdenburg found a markedly delayed combustion of sugar, and Vaughan called attention to the anomalies of protein metabolism in malignant disease. Beneke's work has left its mark on cancer research; it did much to call attention to biochemical factors which had been thought of little consequence. His endeavors to collect comparative statistics concerning the cancer incidence in divers countries, and cities (Germany, Holland, Belgium; Frankfurt, Hamburg, Bremen and the principal towns in Holland and Belgium) show the thoroughly modern trend of his mind, for until then cancer statistics had been concerned practically exclusively with single countries, districts, or cities (Walshe 1844, Sargant 1866, Haviland and Farr 1875, Kiaer 1861-1866) (Hoffman). Davidson's inquiry into the "Geographic distribution" of diseases, 1892, is probably the first attempt at establishing the international distribution of cancer (Hoffman), but systematic national investigation only began in 1900 and lead to a cancer census, which was incomplete "through the indifference of the medical profession" (Wolff). At the time of the Second International Congress for Cancer Research, Paris, October, 1910, a national census had been made for the following European countries: Germany 1900, completed 1907; Holland 1901; Spain 1902; Hungary 1904; France 1908; Greece and Finland 1909; Denmark, to which the honor belongs of having the highest record of microscopic diagnoses (95 per cent) 1910. Beneke died in 1882; it is interesting that his data concerning the relatively high cancer incidence in Holland (especially in the towns of Leyden and Zutphen 1857-1880) have been corroborated by the modern statistics of Hoffman, who shows in his work "The mortality from cancer throughout the world" (1915), that Holland has the second highest cancer incidence.

The wave of controversy which the teaching of Rokitansky and the writings of Beneke produced in Germany extended rapidly to other European countries. In France the constitutional etiology of malignant growth had received consideration long before it had excited any interest in Germany: Andral, Bayle, Cayol and Cruveilhier had been among its earliest exponents.

Paul Broca (1824-1880), the great French surgeon-pathologist, became an enthusiastic believer in the diathesis theories. He was the founder of modern brain surgery and of modern anthropology; in connection with the latter science the statement is attributed to him, "I would rather be a transformed ape than a degenerate son of Adam" (Garrison). His Anatomie pathologique du cancer was "crowned by the Academy" 1852. According to Broca a "constitutional diathesis" was the basis of all malignant growth: "La diathese produit le cancer, celui-ci produit l'infection; l'infection produit les tumeurs secondaires, la cachexie et la mort" (Wolff). It is somewhat difficult to appreciate the exact meaning which Broca attached to the term "infection", as, in the modern acceptation of the word, infection was an unknown entity in his time: it may be safely deduced, however, that he associated it with a progressively increasing perturbation of the "forces metaboliques" which controlled normal diathesis (or in modern terms normal metabolism) and by which the blastema, the starting point of malignant growth, was produced, for Broca still held that "all organised growth is formed at the cost of a blastema" (Wolff). His followers Basin, Guibout and Verneuil tried to define the nature of the diathetic disturbances by classifying them. Basin distinguished between an inflammatory, a hemopoietic, and a heteromorphic diathesis; Guibout suggested that a syphilitic, a scrofulous (tuberculous), a herpetic, and a cancerous diathesis should be recognised as separate entities. Verneuil taught that the cancerous, or neoplastic, diathesis was but the ultimate manifestation of the herpetic diathesis, which in its earlier stages gave rise to eczema, psoriasis, and prurigo; the herpetic as well as the neoplastic diathesis was, according to him, the product of constitutional anomalies transmitted by heredity.

The diathesis theories caused much controversy in England. At a special session of the London Pathologic Society, devoted exclusively to the problems of malignancy (1874), the constitutional origin of cancer was championed by Sir James Paget, while Campbell de Morgan defended the "localised" conception of the disease.

Sir James Paget (1814-1899) was a graduate of St. Bartholomew's Hospital, with which he was associated all his life and was sergeant surgeon to the Queen (Garrison). He was a personal friend of Virchow. In cancer research his name is associated with an original description of eczema of the nipple which is subject to cancerous degeneration (Paget's disease). Garrison says of him, "His life work illustrates how the surgeon proper can be a good clinical observer". It was through the great opportunity for clinical observation which he had that he came to adopt the constitutional conception of cancer: according to him heredity plays an important part in the development of malignant disease, since one out of every three patients suffering from carcinoma had a family history of cancer. Sir James was president of the Royal College of Surgeons and the discussions at the meeting of this society in 1884 showed that the conception of cancer as a constitutional rather than a local disease had gained ground in England. But in England as elsewhere the defenders of the diathesis theories were still handicapped by a lack of biochemic methods and knowledge; they found it impossible to point out any definite, specific factor to which the development might be attributed, because too many problems related to normal growth, and normal physiology remained unsolved at the time; consequently they had to support their contentions by clinical observations and the available imperfect statistics instead of by demonstrable chemical evidence.

Chemistry, although it had developed with unprecedented rapidity, was still the youngest among sciences in the seventh decade of the nineteenth century, for clinical bacteriology was only founded by the culture of the anthrax bacillus by Koch (1877) and the discovery of the staphylococcus and <u>Streptococcus</u> pyogenes by Pasteur (1877-1878). Chemistry, born so to speak with the nineteenth century by the investigations of Lavoisier (1743-1794), had progressed by leaps and bounds. Wohler's synthesis of urea (1825) proving that the products of the body are made of the materials found in "inorganic" nature had been one of the first mile-stones in the progress of chemistry; Kekule's discovery of the open carbon chain and the closed benzene ring had been another (1865); Mendeleeff's periodic grouping of the elements according to their atomic weights had furnished a solid basis of operation for the chemist (1869). It was the development of chemistry through the work of men like Liebig, Salkowsky, Dumas, Graham, Hoppe-Seyler, Fischer and Abderhalden which made possible the life-work of Ehrlich and the achievements of his "chemo-therapy". It was the progress of modern bacteriology on the other hand which gave rise to the numerous "parasitic" theories of malignant growth.

Nepveu (1872) was the first to suggest rather vaguely that cancer might be caused by microörganisms. Discovery of many disease-producing germs during the following two decades seemed to support the assumption that bacteriology would furnish the key to the cancer problem. Even the supporters of the diathesis theories, dazzled by the achievements of bacteriology and overwhelmed by the prestige of cellular pathology, failed to appreciate the full value of chemical investigation. In cancer research chemistry was used sporadically and only by a small number of investigators, although it was proving to be the main spring of progress both in science and in industry.

Paul Ehrlich (1854-1915). Victory over bacterial infection rather than cancer research will forever be associated with the name of Ehrlich. "No better illustration of the practical usefulness of the imagination in creating a working hypothesis can be given than the results achieved by Ehrlich in the field of immunity."* . . . "His sole trend of thought and action was to establish the chemical relationship between tissue cells and chemical agents."** These words, written after his death, summarize his life's work. Cancer research was but a "side-line" in his extensive and indefatigable investigations. Yet his theory of atrepsia, a paraphrase of the biochemic conception of malignant growth conceived by genius, makes him a champion of the metabolic origin of cancer. It is for this reason that I have reckoned Ehrlich among the defenders of the diathesis theories, even though the all-pervading influence of cellular pathology led him in his atrepsia theory to ascribe malignant proliferation to the "avidity of the cell" for nutritive substances rather than to the metabolic conditions which provided these nutritive elements.

A vivid picture of Ehrlich's personality as a man and a scientist has been drawn by his collaborator and friend Wassermann. No one among his contemporaries has known Ehrlich more intimately; for it was with Wassermann that Ehrlich worked for many years in Berlin, but with him also that he discussed in

* Editorial, Jour. Am. Med. Assn., 1915, lxv, 803-804.

** Berlin letter, Jour. Am. Med. Assn., 1915, lxv, 1123.

long letters his work, his plans, his scientific, and financial worries connected with the first salvarsan treatments and with the budget of the Institut für experimentelle Therapie at Frankfurt: a budget which Ehrlich was for ever exceeding. Wassermann described Ehrlich as a "sunny character" and says that it was often hard to decide whether he was speaking in earnest or in jest. His life's motto was, "Be square" (anständig), to which he would add with a twinkle in his eye, "If not from inclination, at any rate from common sense, for squareness alone carries the day". Born at Strehlen, in Silesia, Ehrlich did not give any promise of genius to those who knew him in his youth. He was an indifferent (mittelmässig) student but his love of chemistry showed itself at an early age. Wassermann relates the following characteristic incident. For an important examination (Reifeprüfung) at school a quotation from the German classics "Life is a dream" had been given as the subject of the essay, one of the main features of the examination. Ehrlich proceeded to discuss the statement from the chemical point of view. He suggested that, since life and brain activity both are the result of processes of oxidation, dreams should be looked upon as the product of imperfect oxidation. His teachers, who unfortunately possessed neither a sense of humor nor any enthusiasm for chemistry, failed to appreciate the originality of this argument and the essay was rated as "poor" (ungenügend). Ehrlich carried singleness of purpose almost to an extreme: he was apt to forget everything else when pursuing a train of thought. He had the capacity of genius for observation as well as for taking infinite pains and would detect some barely visible lesion in the papilla of the kidney of a mouse, which his assistants had failed to notice at necropsy, before a microscopic examination had been made. While he was studying the effect of heredity on immunity and its transmissibility through milk he decided to keep the cows used in his experiments under constant observation: keeping cows in Berlin is, however, no small problem: Ehrlich solved the problem by renting a few acres of the elevated railway (Stadtbahn) in the vicinity and by transforming them into temporary stables at his own expense. A fact, not generally known, is that Ehrlich was constitutionally delicate: a severe cold to which he paid no attention proved to be an advanced tuberculous infection; Ehrlich himself was the first to detect the bacillus in his sputum (1888) by means of the staining reaction which he had devised several years earlier. His health at the time was so severely affected, that he was obliged to spend the winter in Egypt; but on his return the newly discovered tuberculin treatment of Koch wrought (according to Ehrlich) a complete cure; he never showed any symptoms of the disease in later years. Ehrlich's life was one of incessant activity and his friends found it well nigh impossible to make him take a vacation even when he seemed at the end of his strength. C. H. Mayo visited Ehrlich a year before his death. He described him as a weary-looking man of medium size, whose hair was turning gray, whose clothes hung loosely around him, suggesting a recent and rapid loss of weight and whose study presented a strange contrast to the methodical methods of investigation, which had made his name famous, as it was a scene of apparently hopeless confusion and untidiness. Books, from which numerous paper markers protruded, manuscripts, and drawings littered every inch of available space: they were scattered all over the floor, piled up on the table and on the only other chair which the room contained beside the one occupied by Ehrlich. The visitor had to pick his way gingerly through this literary chaos while Ehrlich, in order to provide a seat, briskly transferred the volumes occupying the chair to the floor. But during the conversation which followed, Ehrlich again revealed himself as the precise and profound thinker, whose interests embraced every field of research, to whom no detail was too insignificant and whose breadness of vision fascinated his hearer; as usual his cigar, his inseparable companion in his home, his study, and his laboratory was not allowed to go out during the conversation.

The vast scientific researches of Ehrlich were the direct result of an observation made when he was a medical student. He noticed, while working with von Heubel, that in lead poisoning some organs and tissues retained the metal more than others and he found by experiment that these also absorbed the lead when immersed in lead solutions in vitro. This observation became the basis of his work on the chemical affinity between tissues, microörganisms, dyes and reagents. Few men have accomplished more for the progress of science and the good of mankind than Paul Ehrlich: his investigations carried on through nearly four decades are conveniently referred to three periods. Each period represents the work of approximately ten years; it is connected with a theory bearing his name and may be briefly defined as follows: 1877-1888, studies on color-chemistry, which led to the development of the "side-chain"theory; 1889-1899, work on immunity and serum therapy, which gave rise to the theory of "atrepsia"; 1899-1915, the creation of chemotherapy, connected with the theory of the "therapia sterilisans magna", of the one dose treatment, which has not been corroborated by practical experience.

During the first period, in which his work brought him in contact with Frerich, the famous clinician, with Cohnheim, Haidenhain and Welsh, the father of modern American biochemistry, Ehrlich discovered the selective blood stain, which has made him the founder of hematology, the intravital methylene blue staining reaction, the diazo reaction of the urine in typhoid fever, and the "acid-fast" properties of the bacillus of tuberculosis. During the second period, spent in Berlin, he worked with Koch, von Behring and Appolant and proved the chemical relation between toxins and antitoxins by his famous test-tube experiments; it was at this time that, according to Wassermann, "He dreamt of putting serum therapy on a standardized basis similar to that of the metric system" and that he began his investigations on cancer, which led him to demonstrate that cancer can be changed into sarcoma and to suggest that the growth of cancer depends on the presence of certain food substances and immunity from cancer on their absence (atrepsia theory). The third period comprises his activities as director of the Institut für experimentelle Therapie at Frankfurt am Main with his assistants Bertheim and Hatta: his investigations of the sleeping sickness, his discovery of atoxyl and its effect on the malaria parasite, and his victory over the spirochete of syphilis through salvarsan (1910). It is not surprising that the incessant drive, to which Ehrlich's intense and ceaseless activity subjected a constitutionally frail body, led to the exhaustion of vital organs, producing the syndrome of cardiorenal disturbances complicated by arteriosclerosis and diabetes which resulted in his death from heart failure at sixty-one years of age (1915); the effect of mental and bodily strain on the suprarenal glands and the influence of these glands on the heart muscle, the pancreas, and the vascular system are recognized by modern medicine (Barker, Cannon, Crile, Saltykow, Stewart and Rogoff). It is difficult to banish the thought, however, that, had Ehrlich's genius been focused on cancer research as it has been on bacteriologic problems, the words used by Stokes with reference to syphilis might not, even now, be applicable to malignant growth: "The recognition of the disease by the blood test . . . . the treatment and prevention seem built on a firm foundation. As they stand, without regard to future progress, they offer a brilliant future to a campaign of control".

BIBLIOGRAPHY

1. Barker, L.F.: Diseases of the suprarenal glands. Nelson's Loose Leaf Living Medicine, New York, 1920, iii, 215-234.

2. Bazin: Quoted by Wolff, i, p. 315.

3. Broca: Quoted by Wolff, i, p. 182; 314.

4. Cannon, W.B. and De La Paz, D.: Emotional stimulation of adrenal secretion. Am. Jour. Physiol., 1911, xxviii, 64-70.

5. Cramer, W.: Observations on the functional activity of the suprarenal gland in health and in disease. Scient. Rep. Imp. Cancer Res. Fund., 1919, vi, 1-21.

6. Crile, G.W.: Relationship of the thyroid gland to Graves' disease. Can. Med. Assn. Jour., 1917, vii, 727-731.

7. Garrison, F.H.: An introduction to the history of medicine. 2 ed. Philadelphia, Saunders, 1917, 905 pp.

8. Greene, R.H.: Cancer, its nature, causes, diagnosis and treatment. New York, Dougherty, 1918, 172 pp.

9. Guibout: Quoted by Wolff, i, 315.

10. Hoffman, F.L.: The mortality from cancer throughout the world. Newark, Prudential Press, 1915, 826 pp.

11. Hoffman, F.L.: Some new aspects of the problem of cancer control. Minn. Med., 1921, iv, 124-132.

12. Rohdenburg, G.L.: The glycemic reaction in its relation to transplantable malignant tumors. Jour. Cancer Res., 1920, v, 279-289.

13. Rohdenburg, G.L., Bernard, A. and Krehbiel, O.: Sugar tolerance in cancer. Jour. Am. Med. Assn., 1919, lxxii, 1528-1530.

14. Rohdenburg, G.L. and Pohlman, H.F.: Hyperglycemia in its relation to immunity. Am. Jour. Med. Sc., 1920, clix, 853-866.

15. Saltykow, S.: Experimentelle Atherosklerose. Beitr. z. path. Anat. u. z. allg. Path., 1914, lvii, 415-473.

16. Stewart, G.N. and Rogoff, J.M.: Collected papers from the H. K. Cushing Laboratory of Experimental Medicine, 1918-1920, vi.

17. Stokes, J.H.: The third great plague: a discussion of syphilis for everyday people. Philadelphia, Saunders, 1917, 204 pp.

18. Vaughan, J.W.: Blood-changes caused by the hypodermic administration of the cancer proteid. Jour. Am. Med. Assn., 1912, lix, 1764-1769.

19. Vaughan, V.C., Vaughan, V.C., Jr. and Vaughan, J.W.: Protein split products in relation to immunity and disease. Philadelphia, Lea and Febiger, 1913, 505 pp.

20. Vaughan, V.C.: The protein poison and its relation to disease. Jour. Am. Med. Assn., 1913, lxi, 1761-1763.

21. Verneuil: Quoted by Wolff, i, 315.

22. Wassermann, A. von: Paul Ehrlich. Deutsch. med. Wchnschr., 1915, xli, 1103-1106; 1135-1136.

23. Wolff, J.: Die Lehre von der Krebskrankheit, von den ältesten Zeiten bis zur Gegenwart. Jena, Gustav Fischer, i, 1907, p. 488; iii, 1913, 1-201.

THEORIES CONCERNING "ANAPLASIA" AND SPECIFIC CANCER TOXINS

The word "anaplasia" was first used by Haeckel (1866) to designate the sum-total of progressive developments leading to full growth in contrast to "kataplasia", representing all the retrogressive changes which bring about senile decay. Von Hansemann, a pupil of Virchow, introduced the use of this term in the study of malignancy. Ribbert had come to the conclusion that carcinoma is the result of a lack of balance between the growth energy of the epithelium and of the connective tissue, which causes the epithelial elements to proliferate and to invade the stroma. Cohnheim (1839-84) had assumed that malignant tumors develop from dormant embryonic rests which, like Sleeping Beauty, suddenly wake up after many years, sometimes in consequence of traumatic irritation of various kinds, sometimes for no apparent reason. v.Hansemann did not accept Cohnheim's theory; he attributed malignant growth to a special "tendency to proliferation" (Wucherungsreiz), which he does not analyze in detail, but which he holds responsible for the incomplete differentiation of tumor cells. It is this incomplete differentiation to which he refers as anaplasia, evidence of anaplasia being furnished by the divergencies from normal in the nucleus of cancer cells and especially by "asymetric karyokinesis" or abnormal cell division. The term anaplasia, used in a far more general sense than by Hansemann, became the subject of much controversy. Rudolph Beneke, prosector at Braunschweig (1892), not to be confounded with his relative F. W. Beneke, who had died in 1882, stated that anaplastic substances "were contained in all food and could be used for the production of any kind of tissue" (Wolff). According to him the cancer cell was merely an "unhealthy" cell, which proliferated without fully developing and mitotic anomalies were not primary factors but secondary manifestations of the disease condition of the cell. In the end the conception of anaplasia was even made to include the toxic products eliminated by the malignant cell, that is, the substances which supposedly produced the cancer cachexia. During the preceding decades the specific cancer cell had been the object of research, the specific cancer toxin now became the center of interest. The toxicity of disintegration products of tumors had already been emphasized by Aetius of Amida, the "royal physician" of Justinian of Byzantium (600 A.D.), who compared the liquid which could be expressed from tumors to the poison of the most venomous snakes. Lefebure (1784) made a special study of this liquid, "cancer juice" (suc cancereux, Krebsjauche); he found that mixed with extract of violet leaves it gave a red reaction in some types of tumors, not a green one as observed by others. The idea, that cancer cells furnish some specific and deadly poison, was, therefore, time-honored and well-established when Marchand (1902) suggested that the cancer toxin was "the product of the aberration in the cell's vital processes". It was about this time that Griffith isolated a toxic base, which he called Cancroin, from carcinomatous material, and that Spude published the theory which has been named after him (1904); Spude assumed that the cancer toxin "exuded through the blood vessel walls and that it was the real stimulus to cell proliferation which gave rise to anaplasia". It is hard to realise that conceptions such as these were published less than twenty years ago. Kullmann (1904) extracted a markedly hemolytic substance from tumors by maceration with sodium chlorid solution and glycerin: he describes it as "stable on boiling, soluble in water and alcohol, but neither complex nor identical with the ordinary autolytic ferments from normal and cancerous tissues". In France a totally different cancer toxin, colloidal in character, was isolated by Girard and Roger. All of these poisons killed small animals on injection, but none of them caused the development of tumors. Blumenthal's suggestion at the International Cancer Congress (Heidelberg, 1906), that a chemical as well as a histologic anaplasia should be taken into account and that chemical anaplasia was closely connected with the action of enzymes, was, therefore, received with a feeling akin to relief. Interest in a specific cancer toxin died a natural death: the relation of enzyme activity to malignant growth became the chief object of research for a time.

BIBLIOGRAPHY

1. Benoke, R.: Quoted by Wolff, i, 485.

2. Blumenthal: Quoted by Wolff, ii, 22.

3. Girard and Roger: Quoted by Wolff, ii, 29.

4. Griffith: Quoted by Wolff, ii, 28-29.

5. Kullmann: Quoted by Wolff, ii, 28-29.

6. Lefebure: Quoted by Wolff, ii, 28.

7. Marchand: Quoted by Wolff, ii, 28-29.

8. Spude: Quoted by Wolff, ii, 28-29.

THEORIES CONCERNING ENZYME ACTIVITY

SERUM TESTS, CYTOLYSIS, VACCINES, AND PROTEIN THERAPY

"An enzyme is a substance produced by living cells, which acts by catalysis. The enzyme itself remains unchanged in this process, and it acts specifically, that is, each enzyme exerts its activity only upon substances whose molecules have a definite structural and stereochemical arrangement" (Sherman).

Until recently enzymes have generally been looked on as a group of bodies, which are more or less outside the pale of chemical law, unstable, destroyed by temperatures over 60 C (140 F), with very persistent though not unlimited action: in fact, a kind of chemical "free lances", obeying none but their own private rules.

Falk's extensive investigations and his admirably clear monograph, "The chemistry of enzyme action" (1921), furnishes evidence, however, that enzymes notwithstanding their colloidal properties and catalytic activity, conform to the fundamental laws which govern all chemical reactions. Falk says: "Changes in enzyme action afford one of the most sensitive, if not the most sensitive criterion of changes taking place in biologic or chemical material"; and he concludes his monograph with the statement: "The interest in enzymes and enzyme actions from the point of view of life processes is therefore justified, because of their importance as the directive influence in the chemical reactions of living matter".

The idea that enzymes may play a part in malignant growth is barely twenty years old; although the digestion of proteins by the pancreatic juice was observed more than fifty years ago by Willy Kühne (1867), a pupil of Claude Bernard, Professor at Amsterdam and later at Heidelberg. An unknown substance, which he called trypsin was isolated from the pancreas by Kühne (1876) and he proved a year later that this substance, to which he first referred as an "enzyme", is important for the cleavage of proteins during digestion.

The protein character of animal tissues, including malignant tumors, had already been established and accepted. The structure of the protein molecule, the synthesis of certain proteins from their amino acids had been proved by the work of Emil Fischer, when his studies on enzyme activity showed (1894) that enzymes have a selective action, affecting only special proteins to which, as he puts it, "they are related as the key to the lock, or the hand to the glove" (Garrison).

The quest for a specific cancer toxin had proved fruitless. Enzyme activity represented a newly discovered field of research. Small wonder if those who believed that the causative factors in malignancy were furnished by the body itself (as Hunter had suggested more than a century earlier) eagerly turned their attention to enzymes, as products of the organism. It was confidently expected that Blumenthal's hypothesis would be vindicated and that enzymes would prove to be the key to the cancer problem, or at least a means of combating the disease. Unfortunately neither of these expectations has been fulfilled as yet. Blumenthal and Wolff (1905) succeeded in demonstrating that the combined action of hydrochloric acid and pepsin, which readily dissolved normal tissues, did not affect cancerous tissue to the same extent; trypsin, on the other hand, attacked and destroyed cancer cells with seemingly selective action, whereas normal cells appeared to be far more resistant. The injection of pancreatin into tumors, however, by von Leyden and Bergell gave unsatisfactory results: the tumors became necrotic, but the sound, surrounding tissue also suffered, as the poorly stained nuclei showed, and von Leyden discovered that papayotin, the enzyme of the South African paw-paw plant disintegrated cancer cells just as effectively. Neuberg (1904) isolated a new substance, a reducing pentose, by hydrolysis of a large carcinoma of the liver; this type of pentose was not found in normal livers or in other cancerous tissues; although mammary and gastric tumors appeared to contain twice as much nonreducing pentose as normal organs. All of these findings led Rülf and von Leyden to formulate the following distinctly divergent hypotheses.

Rülf's theory. (1906). According to Blumenthal, Rülf's conception of malignancy explained the causation of cancer; it may be summarized as follows: Cancer cells are embryonic cells, consequently they contained an embryonic type of enzyme, capable of attacking diverse tissues, because it carried (like the embryonic cell) many latent possibilities of differentiation; whereas a normal enzyme, the product of a fully differentiated tissue can only attack the specific type of protein to which it is chemically related.

Von Leyden's theory. A totally different point of view was defended by von Leyden and his followers. According to them malignancy developed, not as the result of the composition of the enzymes themselves, but because of the lack of a specific (if hypothetical) force within the organism, which was assumed to regulate both the "hydrolysis" of the enzymes (Fermenthydrolytische Kraft) and protein metabolism. In the absence of this force an abnormal synthesis of the proteins took place, ("abartende" Eiweiss-synthese) which resulted in malignant cell proliferation. Notwithstanding the divergence of the theories which they endorsed, both Blumenthal and von Leyden came to the conclusion that malignancy is a disease of metabolic origin and not a purely local disease; but the enzyme theories were "attacked with great vigor by other research workers" (Wolff). The relation of enzyme action to protein synthesis also furnished material in plenty for dispute. The inadequacy of the methods then available doubtless accounts for the discordant and contradictory findings: the complexity of the chemical reactions involved fully explains why so many of the problems, which became the object of a vast amount of labor and heated argument, are still unsolved today.

During the following seven or eight years numerous enzymes were found and their activities studied, namely: amylase, lipase, oxydase, butyrase, catalase and peroxidase; but it was also discovered that they occurred in both normal and pathologic conditions and in many diverse tissues. Simultaneously a great number of tests were devised for the purpose of determining the nature of the abnormal proteins of tumors or of revealing the enzyme or enzymes especially connected with malignant growth, and many attempts were made to combat malignancy by means of enzymes, serums, and autogenous or foreign proteins. It would be impossible to discuss in detail every one of these tests and treatments for cancer*; only those will be considered which appear to be of historical interest or which are still the object of investigation today (1921); namely, the epiphanin and the meiostagmin reaction, the cytolytic and the serum test, and the therapeutic use of autolysates, serums and proteins. It should further be borne in mind that from 1914 to 1918 the great European War and its aftermath claimed the attention of the whole world; that many eminent research workers had to devote their energies to medical or hygienic problems, when they were not called to active duty; and that many institutes, which had been founded for the express purpose of studying malignant disease had to be used to meet the exigencies created by warfare on a scale without precedent in history. The chemical problems of malignant growth became thus, of necessity and temporarily at least, almost a matter of secondary importance.

Weichardt's Epiphanin reaction (1908). The purpose of this test was to make visible the chemical changes which occur when tissue proteins, protein split products or bacterial proteins are brought into contact with the antibodies produced in disease; the reaction being associated with "changes in the surface tension" (Kolmer); the addition of phenolphthalein and the formation of barium sulfate serve to reveal the acid or alkalin type of the reaction. Jassa and Tokooka (1914) reported that the epiphanin reaction was negative in practically all the noncancerous cases which he studied, and positive in 81.5 per cent of those in which malignancy could be demonstrated. Kolmer, 1917, mentions that Keidel and Hurwitz (1912) obtained sixteen positive reactions in a series of twenty-four serums of persons suffering with definite or suspected malignant disease, but that Burmeister (1915) did not find the test of value in cancer, although it appears to be of considerable value in syphilis.

* A detailed account may be found in Wolff's Lehre von der Krebskrankheit: i, 583; ii, 450-458, and iiib, 458-578.

Ascoli's meiostagmin reaction (1910). The term "meiostagmin", signifying small drops was selected by Ascoli because his reaction is based on the reduction of the surface tension in liquids, revealed by an increase of the number of droplets per cubic centimeter and determined with Traube's stalagmometer. Ascoli observed that the surface tension is reduced when an antigen is mixed with its corresponding antibody. Variations of the number of drops above one, one and a half, or two are regarded as positive reactions; the increase is seldom greater than eight drops (Kolmer). The technic of the test is both delicate and complicated, so that technical errors are only avoided with difficulty. Ascoli and Izar obtained ninety-three positive reactions in 100 cases of malignant tumors and only one positive reaction in 103 nonmalignant conditions (1912), but Burmeister found that negative reactions alone are of some value in excluding cancer. Kolmer (1917) suggests, however, "The method possesses considerable theoretic interest and is worthy of further investigation". Macleod (1920) states "The surface tension between liquid and air is lowered when organic substances are dissolved in the liquid," and "Between solid and liquid the surface tension is always lowered by dissolving substances in the liquid". In the blood serum of patients suffering from carcinoma Robin (1920) found high total nitrogen values and Loeper (1920) an unusual amount of an albumin, which, injected into guinea pigs, produced anaphylaxis for the albumin of cancer; while increased blood sugar values have been reported by Benedict and Lewis (1914), (corroborated by Rohdenburg and Pohlman, 1920), and an abnormal cholesterol content by Luden (1915-1920). These findings suggest, in connection with Macleod's statement, that divergencies in the chemical composition of the blood in cancer may play a part in the positive meiostagmin reactions observed by Ascoli and Izar. It is obvious that an abnormal composition of the blood must be closely associated with or result from metabolic disturbances. Zinsser (1919) says "So far experience with the meiostagmin reaction has not been very extensive", but that "It contains an interesting principle, which with more exact methods of measurement, may well become very important in serum diagnosis". The deduction, therefore, seems admissible that further use of the meiostagmin reaction, combined with chemical analysis of the blood in cancer, may prove of value not only for purposes of diagnosis, but also for the purpose of revealing the metabolic disturbances which underlie malignant proliferation.

Freund and Kaminer's cytolytic reaction for cancer (1910). Freund and Kaminer observed that, whereas normal serum dissolves cancer cells in twenty-four hours during incubation the serum of patients suffering from carcinoma fails to destroy the cancer cells. The reaction shows that normal serum either contains some cytolytic substance which cancer serum lacks or that the cancer serum has certain ingredients which protect the cancer cell from dissolution. P. von Monakow (1911) made an intensive study of the reaction. He corroborated the protection of cancer cells by cancer serum, but found that 25 per cent of normal serums behave like cancer serum and inhibit the destruction of cancer cells during incubation. The question suggests itself whether continued observation over long periods of the persons whose serum behaved like cancer serum might not have revealed an eventual development of malignancy; evidence confirming this suspicion would have furnished a valuable clue concerning the chemical or metabolic disturbances which pave the way for malignant growth. Koritschoner and Morgenstern (1920) revived the study of the cytolytic reaction (which had become more or less discredited) by introducing a new technic connected with the use of the refractometer. Preliminary investigations had convinced them that the "degree of disintegration" of the cancer cell after incubation with normal serum was largely a "matter of personal opinion", but that more conclusive evidence might be obtained if an increase of the refractory index occurred when normal serums acted on cancer cells. Since it is known that the refractivity of liquids increases when substances are dissolved in the liquid, an increase of the refractory index of the normal serum after incubation with cancer cells might prove that part of the cells had been dissolved into the serum, thus augmenting its index. Experiments conducted with (1) serum alone, (2) cancer cells in normal salt solution, (3) cancer cells in normal serum, and (4) cancer cells in cancer serum corroborated the observations of Kaminer and Freund, a much higher refractory index being obtained when cancer cells were added to normal serum than when cancer cells were combined with cancer serum. Several other important facts were revealed by the modified technic of Koritschoner and Morgenstern. Their findings may be summarised as follows: (1) the index of refraction is increased when cancer cells are used in combination with normal serum and with the serum of feverish but cancer-free patients, even when the serum of the latter has been inactivated; (2) the refractory index remains unaltered when cancer cells are used in combination with the serum of fever-free cancer patients; (3) the refractory index is reduced when cancer cells are added to the serum of feverish patients suffering from carcinoma, or to inactivated normal serum; and (4) it is also reduced when normal liver cells, instead of cancer cells, are added either to normal serum, to the serum of feverish but cancer-free patients, or to the serum of feverish patients suffering from carcinoma. Koritschoner and Morgenstern further observed that coagulation of the cancer cells reversed the type of the refractometric changes produced, whereas De Crinis and Pregl (1914) had reported that the coagulation of cancer protein increased the refractivity of cancer serums. Apart from the anticytolytic action of cancer serum in the absence of fever, the most important of these observations seems to be the similarity between the effect of inactivated normal serum and of cancer serum during febrile reactions, both lowering the refractory index, whereas the index is increased by normal serum during febrile conditions even after inactivation. The anticytolytic action of cancer serum in the absence of fever points to the absence of some substance or substances by which cytolysis is brought about, as much as to the presence of some ingredients by which cytolysis is prevented, lack of assailants eliminating danger as effectively as the assistance of protectors. By "inactivation", a process during which something in the serum is eliminated or destroyed, normal afebrile serum is reduced, so to speak, to the level of cancer serum under febrile conditions; although the serum of noncancerous, but feverish, persons retains its characteristic properties despite "inactivation". All of these facts seem to point to a fundamental imbalance within the organism in which cancer develops; they appear to justify the conclusion that the metabolic disturbances which promote or cause this imbalance may also play a prominent part in promoting the lawless proliferation of cells.

Abderhalden's serum reaction for cancer (1912). The rapid mobilization in the body of specific enzymes or ferments, intended to facilitate the assimilation of the corresponding proteins, forms the theoretic basis of this reaction. Abderhalden observed in his earlier experiments, that when egg albumin, horse serum, silk peptone or other substances are injected into dogs or rabbits, the blood serum of these animals develops a definite proteolytic action for the substances injected, which it does not possess before injection. These findings led him to study the reaction between the protein of the placenta and the blood serum in pregnancy, and between the protein of tumors and the blood serum in malignant disease, because, according to him the mobilisation of specific enzymes was likely to occur, the placenta being a temporary structure within the organism and the tumor an altogether abnormal constituent of the body. He obtained what appeared to be specific proteolytic reactions in both instances. The technic which he devised comprises two methods, the dialyzation and optical method; both methods are complicated and the results likely to be falsified by "errors beyond the immediate control of the serologist" (Kolmer). Levin and Van Slyke (1915) applied a quantitative method to Abderhalden's serum test for cancer and came to the conclusion that "the diagnostic value is doubtful to say the least" and that "the test belongs to the laboratory rather than to the clinic". According to Zinsser (1919) the supposedly specific enzymes react with diverse substances belonging to the same chemical group, so that "as the final result of these extensive and intricate researches we have merely a better understanding of the nonspecific activity of normal serum". It should be mentioned, however, that A. Robin (1919), professor of clinical therapeutics of the University of Paris, who made the biochemic problems of malignant disease the object of numerous analyses and comprehensive investigations expressed the opinion, that cancer is a "ferment disease". According to him the dissociating action of a "double or almost triple proteolytic ferment in the tissues around the cancer, not in the cancer itself", serves to furnish to the cancer cells those products of proteic dissociation with the aid of which they grow and multiply; chief among these products are the amino acids which Mendel and Osborne regard as growth elements (hexonic bases), which give to the cells a tendency to rapid growth and anarchistic multiplication, the very rapidity of their growth not leaving them time for differentiated evolution. A similar conception of malignant growth, but connected with the metabolism of food rather than with tissue ferments, is contained in the writer's suggestion (1917): "Would it be reasonable to deduce from the foregoing facts*, that substances supplied in the food and insufficiently metabolised by inadequate organs could become the cause of lawless proliferation; inasmuch as the daily intake of (imperfectly metabolised) food would furnish a constant stimulant, that might bring about a hurried coinage of unfinished, atypical cells, embryonic in character, simply because the rate of production did not allow them time to become full-grown?" The body itself would thus furnish "the conditions by which proliferation is either regulated and kept within normal bounds or incited to become lawless and destructive".

<u>The therapeutic use of tumor cell emulsions, (vaccines), serums and proteins.</u> The foregoing methods of investigation seemed well calculated to further the solution of the cancer problem; they appeared to be in harmony with certain biologic laws which are dimly perceptible in immunity reactions. The various therapeutic measures to which they gave rise represented methods of attack

* Observations in dietary experiments.

which had proved successful in germ-born disease, even if no conclusive evidence had been produced, showing that either bacteria or protozoa had something to do with the development of malignancy. Cell inclusions, simulating parasites (Plimmer's and Russell's bodies) had been recognised as mere artefacts (Spirlas, 1903, Greenough, 1905). Russell (1908) who summarised the results of countless experiments on tumor bearing animals, had already come to the conclusion that there were no features in the immune condition (to tumor transplants) comparable to the antibodies evolved against infective organisms" (Woglom).

Jensen, "the Pasteur of cancer research" (Wood), was the first to try the effect of emulsions of tumor cells on tumor bearing animals (1909); in some cases the tumors receded following the injections, in others central necrosis of the graft could be observed, but malignant growth seemed to be promoted rather than retarded, for an unusual crop of metastatic growths would often be found in distant organs. Blumenthal and Lewin (1912) reported striking results with emulsions made from a special strain of rat sarcoma; Lewin obtained no less than 80 per cent of regressions and 35 per cent of "cures", but emulsions made from a different tumor strain only produced 35 per cent of regressions and barely 10 per cent "cures". Blumenthal laid great stress on technic used in preparing the emulsion: he recommended freshly-made emulsions, incubated at body temperature only, "chloroform-water" being used as preservative and for the purpose of destroying the vitality of the cells. Lewin used toluol for this purpose. Stammler (1919) introduced the use of intravenous injections, prepared with normal salt solution after careful grinding of the cells in a mortar and reported satisfactory results with this technic in cases of inoperable carcinoma in human beings. Lunckenbein (1914) corroborated Stammler's findings and called attention to the fact, that severe systemic reactions, chills, fever up to 104° and even transitory collapse, always occurred in patients who responded to the treatment. The possible therapeutic value of such systemic reactions themselves, regardless of the type of treatment by which they are produced, will be considered in connection with results reported following the use of serum or proteins. Fischera (1912) suggested the substitution of tumor cells by embryonic tissues, because tumors rarely develop during fetal life or during infancy and the assumption therefore seemed justified that embryonic cells contained elements capable of checking neoplasia. He had also found that mice could be rendered refractory to grafting through injections of the macerated cells of mouse embryos; such injections, moreover, caused the disappearance of tumors in 82 per cent of the tumor bearing rats, of which only 50 per cent responded to tumor cell emulsions. Fischera reported satisfactory results in thirty-nine cases of sarcoma in human beings, including 15 per cent of cures; Uffreduzzi, Betti and Bazzocchi also observed a marked improvement in the condition of the patients following the use of emulsions made of fetal tissues, but other workers have been unable to corroborate these findings.

The so-called "autovaccines", first used by Coca and Gilman (1909) were but slightly modified emulsions, made by crushing and centrifugalizing an excised portion of the patient's tumor, a suspension of which was injected subcutaneously: the remainder of the tumor disappeared through reabsorption after the injections. The term "vaccine" is a misnomer, according to modern terminology, since no devitalized bacteria, but merely devitalized cells were employed. Odier (1913) recommended the use of a "vaccin antineoplastique hypersensibilise" at the Third International Congress for Cancer Research at Brussels, where he exhibited photographs of patients, who appeared to have been cured by this method of treatment. The remedy which he advocated combines the properties of vaccine and serum therapy: a small amount of the patient's blood, sufficient to yield a few cubic centimeters of serum, is mixed with a portion of the patient's tumor which has been carefully crushed and heated to 56 C. Twenty-four hours after subcutaneous injection of this mixture some more of the patient's blood is taken and the serum added to the remaining portion of the tumor emulsion, which is then allowed to stand for twenty-four hours and mixed with normal serum; the resulting "vaccin hypersensibilise" is injected in very small doses; large doses are apt to give dangerous symptoms and the reaction produced serves to indicate the "pouvoir leucostimulant" of the preparation as well as the response of the patient and all symptoms of systemic disturbance must have disappeared before the injection is repeated. The results reported by Odier at the Congress in Brussels make it hard to understand why his method should not have been given a further trial by other workers after August, 1913; it may be that the World War (August, 1914) prevented continued observation, especially as previous attempts with autovaccines (Werner, 1911) made at the Institute for Cancer Research at Heidelberg had apparently discredited the use of vaccines.

Serum and protein therapy. These two diverse types of treatment will be discussed together, because there appears to be a fundamental similarity in their action, namely the stimulation of metabolic functions by the introduction of foreign protein. This stimulation of metabolism as a whole is revealed by a chain of phenomena, fever, changes in blood pressure, nausea, edema, pain in the joints, and cutaneous eruptions, the so-called anaphylactic reactions. The severity of the reaction as well as its predominant symptoms depends partly on the protein used, partly on the individual chemistry of the recipient. The reaction itself, however, is the result of a more or less violent "stirring up" of the body as a whole; this fundamental fact will be admitted, no matter which of the numerous theories dealing with anaphylaxis (Vaughan, Friedberger, Weil, Doerr, Coca and others) may be given preference or finally proved correct. If, as I have suggested*, malignancy be caused by inadequate or reduced metabolic processes, many factors, each capable of activating the body chemistry, may be expected to improve malig-

* Studies on Cholesterol V.: "It will also be remembered that the process of spontaneous regression of malignant tumors, whether the tumors be grafted or of autogenous growth, is usually accompanied by ulceration, "sloughing" or hemorrhage; that radium treatment produces these symptoms as well as a "general reaction" in many cases; that acute bacterial infections (such as erysipelas, for example) often exert a curative influence on the growth of tumors and that the rate of basal metabolism is manifestly increased by all of these factors, as shown by the accompanying febrile reaction".

nant conditions. The fact that totally different types of treatment and even intercurrent diseases are known to have exerted a beneficial effect on malignant growths, seems to support this view: Coley's treatment, radium therapy, the results reported by Vaughan, and the influence of erysipelas need only be recalled. In Chapters VIII and IX this point will be discussed at greater length. Meanwhile the foregoing considerations seem capable of explaining both the results and the failures of serum and protein therapy; the individual chemistry of the recipient at the time of treatment, that is, the ability of divers organs to respond to stimulation, must be largely responsible for the effects produced, in a given case.

Serum therapy, or passive immunization, was inaugurated by Behring's successful treatment of diphtheria (1890). Lack of conclusive evidence concerning any bacterial agency in malignant growth suggested a priori that serum therapy would be powerless in malignant disease. Kolmer's definition "In passive immunization our own body cells do not produce the antibodies, but we receive them passively in the form of antibody-laden serum; the antibodies are produced by active immunization of some other animal . . ", will be recalled in this connection. A number of observations, however, seemed to indicate that serum treatment might influence malignant growths. Richet and Héricourt (1895) who were the first to try this method of treatment, reported that they had obtained a marked improvement following injections of the serum of a donkey, which had been immunized repeatedly with emulsions of a nonulcerating sarcoma; but they had to admit "que cette amelioration ne va pas jusqu'a la guerison". Gaylord, Clowes and Baeslack (1905) found that injections of the serum of mice, in which transplanted adenocarcinoma had regressed spontaneously, rendered other mice refractory to grafting; and that the serum of animals with spontaneous tumors had a similar effect, even when there was no regression. Vidal (1910) pointed out that any kind of serum might be expected to produce these results to a certain extent, since Kolling (1903) and Edel (1908) had obtained an improvement in the condition of patients by using placental as well as normal defibrinated blood. Hodenpyl (1908) observed that both the production and the reabsorption of ascites and transudates were accompanied by tumor regression in malignant conditions. He, therefore, treated forty-seven patients suffering from carcinoma with intravenous injections of ascitic fluid; the results were encouraging, in the majority of cases; the tumor cells disintegrated, the normal tissues did not seem to be affected. Lewin (1913) reported similar results, but others (Ill and Miningham, 1912, for example) could only obtain a reduction of pain and hemorrhage and a slight general improvement, although they mention finding antibodies in the ascitic fluid of patients suffering from malignancy. A "new antiserum for cancer" was introduced by Berkeley (1915). This serum was obtained by injecting the extract made of the patient's tumor, after its operative removal, into normal sheep. Berkeley states that "antibodies, demonstrable by complement fixation test" were found in the serum of the sheep, and that marked improvement of the general condition of the patients followed injection of the sheep serum, although "the effect of the remedy upon extensive, inoperable growths . . . is palliative and temporary". He explains the action of the serum as follows: "Being itself a proteid substance, the antiserum automatically excites in the patient's tissues the formation of auto-antibodies" and adds that no success is to be expected if frequent and overwhelming injections do no good in two or three weeks.

No definite cures could be reported by Berkeley after observations extending over three years and no further reference to his method of treatment could be traced in the literature after 1915. It is of interest, however, that investigations concerning serum treatment in malignancy are still being carried on at the present day; witness the recent observations of Drügg and Pesci. Drügg (1920), who is connected with the university clinic of Cologne, studied the effect of the serum of horses, which had been sensitized with different tupes of tumors. In order to ascertain which serum would be most suitable, a portion of the patient's tumor was excised and tested according to Abderhalden's technic: autolysis of the tumor was taken to indicate the type of the patient's "blood reaction" and the serum selected accordingly. Drügg reports one definite cure and four failures as the result of this procedure; but certain facts mentioned by Drügg in connection with these failures are noteworthy, although Drügg does not seem to have been impressed by them, as he does not discuss them. The patient, who responded to the treatment, was a woman aged forty-three, suffering from a scirrhous cancer of the breast with extensive glandular involvement, the left arm being contracted and paralysed by pressure on the brachial plexus. She had in addition " a plum-sized nodule in the left mamma". Her test showed no autolysis for mammary carcinoma. The treatment, consisting in intramuscular injections of a "scirrhous serum", was begun in 1917. A severe systemic reaction followed with fever up to 103. Six weeks later the nodule in the left breast had vanished completely. The blood test now showed autolysis of fibro-adenoma and a faint autolysis of mammary cancer. Some suppuration occurred, which lasted till 1918. When last seen, 1920, the patient's general health was excellent; she looked well; only a faint scar and no trace of tumor formation could be detected, although the paralysis had not receded. The other four patients, three men and one woman, all died in from three to six months after treatment, but the following data are found in their histories: They were about ten years older than the woman who was benefitted by the treatment; the autolysis tests showed a reaction with wholly unrelated types of malignancy; the serum used for treatment did not correspond either to the type of autolysis or to the type of malignancy from which the patient was suffering. Thus, the woman was given injections of "squamous cell serum", whereas she was suffering from an ulcerating mammary cancer with glandular involvement; one of the men had a spindle-cell sarcoma with glandular involvement, and the Abderhalden test revealed a faint autolysis for cancer of the gallbladder and a marked autolysis for "carcinoma solidum mammae", the other man had a squamous-cell cancer of the lower lip, the test showed slight autolysis for a "small cell carcinoma" and marked autolysis for a "Hierenendothel

(?) krebs". Both men, however, were treated with a "oesophagus serum". In thirteen cases of unquestionable carcinoma, five gave no reaction to any of the several types of serum which were tried; six cases of gastric cancer reacted to homologous serums; a suspected gastric carcinoma gave a reaction with cancer of the gallbladder and with gastric adenocarcinoma, although no cancer could be found at necropsy; seven normal persons showed no reaction whatever to any of the numerous serums used. These data have been given somewhat in detail as they may furnish a clue for further investigation. It is conceivable that a minute chemical analysis of the blood of these patients might have revealed chemical differences in the ratio, for example, between the globulins, the serum albumin and the lipoids; differences, which in turn might help to explain the beneficial effect of scirrhous serum on a scirrhous cancer and the lack of response to treatment in the other cases.

Pesci's researches were made at the Radium Institute of the University of Turin. They were intended "to reveal, if possible, the hypothetical antigen in cancerous blood"; they include experimental work, and therapeutic and clinical observations. In the experiments guinea pigs were "sensitised" with the supernatant fluid of a tumor emulsion, which had been prepared by mixing the tissue with ground glass and normal salt solution, extraction being carried on for twenty-four hours at a temperature below zero. The animals were sensitised with minute doses which produced no immediate reaction. Three weeks later intracardial injections of either tumor emulsion, normal serum, or the serum of patients suffering from cancer were given. The injections produced no symptoms in the nonsensitised controls; the sensitised guinea pigs all died, hemopericarditis, anaphylactic icterus, and pulmonary edema being found at necropsy. Pesci admits that these findings were to be expected; they are in accordance with all observations on anaphylactic reactions in which diversity of species plays a far greater part than diversity of organs or tissues. But he adds, that he is led to deduce from his findings, "that cancer cells represent a modified type of cells". This is universally conceded; it seems a foregone conclusion if malignancy is interpreted as the result of metabolic anomalies. If, as is well known, potatoes grown on sandy soil differ materially from potatoes grown on clay soil (even when they come from the same original stock), cells growing under abnormal chemical conditions cannot but differ from cells grown under normal conditions. It is difficult to see, however, how the anaphylactic reactions produced by Pesci could furnish any evidence concerning the abnormality of cancer cells, no matter to what cause the deviation from normal be attributed. Pesci further endeavored to establish whether or not the beneficial effect of radium in malignancy might be connected with the production of antibodies. The blood serum of a patient, in whom a uterine cancer had disappeared under radium treatment, was used for injections into another patient, who was also suffering from carcinoma of the uterus. No beneficial effect could be observed. However, the patient whose blood was used and who appeared to respond to radium treatment, suddenly developed extensive retroperitoneal metastasis which proved fatal. It is, therefore, reasonable to assume, as Pesci suggests, that if any antibodies had been produced, the amount must have been too small to have any effect on injection, since it was not even sufficient to safeguard the patient, who had apparently been cured. In the course of his investigations Pesci made an important observation: he found that of eighteen patients treated with radium for malignancy six had positive Wassermann reactions which became negative under the influence of radiotherapy. He suggests that two hypotheses, both based on previous work done in connection with the mechanism of the Wassermann reaction, may help to explain this phenomenon. The first hypothesis deals with the globulin-albumin ratio in positive and negative Wassermann reactions. Pesci considers, that, since there is evidence that the globulins are changed qualitatively when complement fixation occurs, and since Ronchese found that the addition of normal serum caused syphilitic serum to lose its inhibitory action because of an excess of albumin in normal serum, the liberation of albumin by the radium rays may account for the changes which he observed. The second hypothesis deals with the relation of the blood lipoids to complement fixation. Pesci expresses the opinion that the globulin-lipoid complex (the lipoids attached to the globulins) plays the most important part in the Wassermann reactions. He quotes the following findings in support of this view. Cholesterol, a blood lipoid, furthers complement fixation; the addition of ether, a lipoid solvent, to syphilitic serum produces a positive Wassermann reaction in the absence of an antigen (Pick and Pribram); which proves that the ether so modifies the serum as to endow it with antigen-like properties. Mechanical destruction of part of the liver or brain in normal animals is followed by complement fixation (Bittorf and Schidorsky); as the result of a discharge of lipoids into the circulation, according to Pesci. Complement fixation is known to occur after ether anesthesia (Rabinowitch, 1913) and ether anesthesia causes an increase of lipoids in the blood (Catteretti, 1914). Hypercholesterinemia alone does not produce complement fixation (Henes, 1915); low cholesterol values were found to prevail in the blood of syphilitics by Carbone and Nizzi (1913), their observations being corroborated by Piazza (1916), who also reports the prevalence of high cholesterol values in malignant conditions. Browning (1912), on the other hand, obtained complement fixation in the blood of normal animals by addition of cholesterol and lecithin extracted from the heart muscle of an ox. The sum total of this evidence tends to show, according to Pesci, that the combination of globulins and total blood lipoids plays an important part in the Wassermann reaction.

Although the work of these Italian investigators was unknown to me, my studies on the blood cholesterol (1915-1920) gave results, which are in harmony with their findings. Determinations on about 3,000 individual blood samples led me to observe an increase of the blood cholesterol after ether anesthesia, low or medium values*, in syphilis and a preponderance of high values in carcinoma, whereas in sarcoma the blood cholesterol was found to be normal or but slightly in-

* Bloor's methods were used; normal values by the Bloor I method are from 70 to 100 mg. for each 100 c.c. of whole blood; medium values from 100 to 140 mg., high values above 140 mg.

creased. The changes in the blood cholesterol following radium treatment, which I reported, may have a bearing on Pesci's findings concerning the effect of radium on the Wassermann reaction. A marked increase of the blood cholesterol values is commonly found in conditions such as pregnancy, acute infections, malignancy and during the digestion of a heavy meal; conditions in which "spurious Wassermanns" have also been observed. Bacterial invasion, with the exception of tonsillitis, typhoid fever, and mild infections, is accompanied by a marked rise in the blood globulins, according to Rowe; although he could not establish any relation between the increase of the globulins, and the Wassermann reaction. Tokuda's (1921) refractometric studies demonstrated, however, "When the Wassermann reaction remained persistently positive, the refractive index, the percentage of total proteins and the relative amount of globulins, showed little or no tendency to drop below their original values"; whereas, "When the Wassermann reaction . . . became very readily negative, the curves fell with more or less regularity during the course of injections". The independent and simultaneous observations of Bircher and McFarland gave similar results. Bircher and McFarland state, "Viscosity and refractometry depend on the water content of the blood and the total proteins"; Tokuda cautiously suggests, "In syphilis and perhaps also in other infections, it may be assumed that these increases (in refractive index and relative amounts of serum proteins) are really due in part or entirely to an augmentation of the lipins (cholesterol, lecithin, and so forth), which are bound in strong chemical union with the serum proteins".

In view of these findings and of Pesci's data on changes in the Wassermann reaction in malignancy under radium treatment further investigations embracing simultaneously the blood lipoids and the blood globulins would seem of the utmost importance. Such investigations would be well calculated to throw light on the problems of both complement fixation and malignant growth. They might also help towards getting a clue to the metabolic disturbances which underlie malignant proliferation and the organs by whose inefficiency these disturbances are brought about. Divergency of reaction and dissimilarity in changes of the blood chemistry shown by patients either under radiotherapy or during treatment for syphilis might thus be traced to a greater or less power of response to stimulation in one or other of the endocrine glands.

Protein therapy in its most comprehensive acceptation, including the use of autolysed tissues, serums, and foreign proteins, has been employed in numerous and dissimilar diseases: injections of embryonic cells were used by Fischera, milk has been injected intravenously in typhoid fever and intramuscularly in influenza (Thirloix); satisfactory results have been obtained in a number of cases, but not in all.*

In a recent survey of the "Non-operative treatment of tumors" the great surgeon Bier (1921) expresses the opinion, that his twenty years' experience with protein therapy has convinced him that injections of foreign protein, especially pig's blood, often give surprisingly good results, whereas resection far into the sound tissues in cases of incipient, localised cancers of the mouth, the breast, or the stomach without glandular involvement, may be promptly followed by such extensive recurrences, "that it seems as if the operation had whipped up the malignant process"; he therefore recommends injection of blood followed by exposure to roentgen rays in the treatment of early carcinoma.

Danysz (1921), head of the Pasteur Institut in Paris, has called attention to the fundamental, physicochemical principle, which underlies the evolution of disease, namely, the formation, in diseases amenable to serum therapy (diphtheria, tetanus) of soluable, salt-like compounds, which dissolve in an excess of antibody, as contrasted with the formation of insoluable compounds, colloidal in character, which by clogging the smallest capillaries produce the anaphylactic manifestations of the diseases that have proved refractory to serum treatment

* Repeated intraperitoneal injections of boiled cancerous mouse tissue produced immunity in 80 per cent of the experimental mice, when the controls gave 100 per cent of takes (L. Kepinow, 1920). These findings throw light on the results of "actual cautery", causing protein reabsorption.

(typhoid, tuberculosis, influenza). With characteristically French vividness of terms Danyez refers to anaphylaxis as "intra-cellular or intra-vascular indigestion", showing that the experiments of Besredka and Roux, which present "very complex phenomena . . . almost impossible to interpret", prove conclusively, that in animals anaphylactic shock may be prevented by the use of narcotics. It is worth remembering in this connection that the effect of drugs (that is, pharmacologic preparations in general) on the activity of the endocrine glands has received scant consideration so far. Sajous (1919) appears to correlate the known action of drugs with the altered activity of the glands of internal secretion. The evidence which he presents is based chiefly on earlier investigations and does not include the work of Stewart and Rogoff (1919); the findings of those physiologists, however, obtained by perfected method, lend support to the conceptions of Sajous, showing, for example, that strychnin stimulates adrenal activity and increases the epinephrin-output from ten to a hundred-fold even after transsection of the cervical cord; whereas this effect of strychnin is abolished by removing one adrenal and nervating the other. Nor is further evidence lacking. Sajous suggests that morphin influences the activity of the adrenal glands and that "morphinisms" is the result of their depletion. It is known that both morphin and ether anesthesia increase the blood cholesterol values, which play a part in bacterial infection and which are controlled to a great extent by the suprarenals. It is obvious, as I have suggested elsewhere, that the chemical changes in the blood as well as the response to treatment will differ materially in two patients, one of whom, for example, has an active thyroid and damaged, inefficient adrenals, whereas the other happens to possess active adrenals but a more or less inadequate thyroid gland. This may seem a foregone conclusion, but it does not seem to be taken into account in connection with either the effect of drugs and response to treatment, or clinical and laboratory findings. The factor of endocrine response may, however, prove of value for the interpretation of phenomena, such as the prevention of anaphylactic shock by narcotics and the results obtained by protein therapy.

Kross' (1921) studies on immune bodies in malignancy should be mentioned here. His first series of experiments showed that blood transfusions from resistant animals do not produce immunity in susceptible ones. He concludes that "Immune bodies if such exist are not resident in the circulating blood"; he adds, "The possibility that the injections acted as nutriment could be discarded, but mentions that they 'accelerated' tumor growth and warns against transfusions in 'human cancers'". If any nutritive action is to be excluded the accelerating influence and the warning against therapeutic transfusions are decidedly surprising. The second experimental series proved that parabiosis of resistant and susceptible animals affects neither susceptibility nor resistance, but that the condition of the animals following parabiosis lessened the rate of tumor growth.

The investigations of Kópinow (1921) who obtained immunity to inoculation in 80 per cent of the mice which had been injected intraperitoneally with boiled cancerous mouse tissue, whereas the controls furnished 100 per cent of takes, recall the results obtained by protein therapy as well as the beneficial effects of the actual cautery; since the reabsorption of the protein derivatives and their stimulating influence on metabolism in general undoubtedly played a part in the success of the experiment which he describes.

BIBLIOGRAPHY

1. Abderhalden, E.: Die serodiagnostik der Schwangerschaft. Deutsch. med. Wchnschr., 1912, xxxviii, 2160-2163. Quoted by Wolff, iii, p. 538.

2. Ascoli, M.: Die spezifische Meiostagminreaktion. München. med Wchnschr., 1910, lvii, 62-63.

3. Ascoli, M. and Izar, G.: Die Meiostagminreaktion bei bösartigen Geschwülsten. München. med. Wchnschr., 1910, lvii, 403-405.

4. Ascoli, M. and Izar, G.: Giftbildung durch Einwirkung von Blutserum auf art und körpereigene Organextrakte. München. med. Wchnschr., 1912, lix, 1092.

5. Bazzocchi, A.: Sulla istoterapia dei tumori maligni dell'uomo. Tumori, 1913-1914, iii, 364-370. Quoted by Wolff, iiib, p. 575.

6. Behring: Untersuchungen über das Zustandekommen der Diphtherie-Immunität bei Thieren. Deutsch. med. Wchnschr., 1890, xvi, 1145-1148.

7. Benedict, S.R. and Lewis, R.C.: The sugar content of the blood in cancer. Med. Rec., 1914, lxxxvi, 650.

8. Berkeley, W.N.: Some comments on a new antiserum for cancer. New York Med. Jour., 1915, cii, 45-47.

9. Besredka and Roux: Quoted by Danysz.

10. Betti, O.: Contributo alla terapia istogena dei tumori maligni. Tumori, 1912, i, 450-454. Quoted by Wolff, iiib, p. 575.

11. Bier, A.: Versuche über nichtoperative Behandlung von Geschwülsten, mit besonderer Berücksichtigung der "Proteinkörpertherapie". München. med. Wchnschr., 1921, lxviii, 415-418.

12. Bircher, M.E. and McFarland, A.R.: The globulin content of the blood serum in syphilis. Arch. Dermat. and Syph., 1922, v, 215-233.

13. Bittorf and Schidorsky: Quoted by Pesci.

14. Blumenthal, F.: Ueber Heilungsversuche bei einem Rattensarkom. Med. Klin., 1910, vi, 1982-1984.

15. Blumenthal, F. and Wolff, H.: Ueber Fermentwirkungen bei Krebsgeschwülsten. Med. Klin., 1904-1905, i, 166-168. Quoted by Wolff, ii, 22.

16. Browning: Quoted by Pesci.

17. Burmeister, W.H.: The meiostagmin and epiphanin reactions in the diagnosis of carcinoma. Jour. Infect. Dis., 1913, xii, 459-471. Quoted by Kolmer.

18. Carbone and Nizzi: Quoted by Pesci.

19. Cattoretti: Quoted by Pesci.

20. Clowes, G.H.A.: Preliminary communication regarding an immune body capable of inhibiting the development of cancer in mice (adeno-carcinoma, Jensen). Bull. Johns Hopkins Hosp., 1905, xvi, 130-132.

21. Clowes, G.H.A. and Baeslack, F.: Further evidence of immunity against cancer in mice after spontaneous recovery. Med. News, 1905, lxxxvii, 968-971. Quoted by Wolff, iii, p. 556.

22. Coca, A.F. and Gilman, P.K.: The specific treatment of carcinoma. Philippine Jour. Sc., 1909, iv, 391-402. Quoted by Wolff, iiib, p. 564.

23. de Crinis, M.: Dialysierversuche mit der von Pregl vereinfachten und modifizierten Methode von Abderhalden und die klinischen Befunde. Fermentforsch., 1914, i, 13-19.

24. Danysz, J.: The evolution of disease. Philadelphia, Lea and Febiger, 1921, 194 pp.

25. Drügg, W.: Zur Immundiagnostic- und Therapie des Karzinoms. Zentralbl. f. Chir., 1920, xlvii, 1198-1202.

26. Edel: Quoted by Wolff, iiib, 558.

27. Falk, K.G.: The chemistry of enzyme actions. New York, Chemical Catalog Co., 1921, 136 pp.

28. Fischer, E.: Die Chemie der Kohlenhydrate und ihre Bedeutung für die Physiologie. Berlin, G. Lange, 1894, 38 pp. Quoted by Garrison.

29. Fischera, G.: Sui recenti contributi alla dottrina dei neoplasmi. Tumori, 1911, i, 1-74. Also: Ann. del r.Ist. di Clin. Chir. di Roma, 1912, iv, 141-190.

30. Fischera, G.: The biological treatment of cancer. Jour. Cancer Res., 1918, iii, 303-319.

31. Freund, E. and Kaminer, G.: Ueber die Beziehungen zwischen Tumorzellen und Blutserum. Biochem. Ztschr., 1910, xxvi, 312-324.

32. Freund, E. and Kaminer, G.: Ueber karzinolytische organische Säuren. Wien. klin. Wchnschr., 1919, xxxii, 1105-1107.

33. Garrison, F.H.: An introduction to the history of medicine. 3 ed. Philadelphia, Saunders, 1921, 942 pp.

34. Greenough, R.: Quoted by Wolff, i, p. 675.

35. Hess, E., Jr.: Cholesterinemia and the Wassermann reaction. Jour. Am. Med. Assn., 1915, lxiv, 1969-1972.

36. Héricourt, J. and Richet: De la sérothérapie dans le traitement du cancer. Compt. rend. Acad. d. sc., 1895, cxxi, 567-569. Quoted by Wolff, iiib, p. 548.

37. Hodenpyl: Quoted by Wolff, iiib, p. 566.

38. Ill, E.J. and Miningham, W.D.: An experimental study of the treatment of cancer with the body fluids. Jour. Am. Med. Assn., 1912, lix, 497-502.

39. Isar, G.: Ueber eine spezifische Eigenschaft luetischer Blutsera. München. med. Wohnschr., 1910, lvii, 182-183.

40. Jensen, C.O.: Ueber einige Probleme der experimentellen Krebsforschung. Ztschr. f. Krebsforsch., 1908-1909, vii, 279-285. Quoted by Wolff, iiib, p. 568.

41. Jensen, C.O.: Quoted by Wood.

42. Jousa, E. and Tokooka, M.: Untersuchungen über die Epiphaninreaktion bei Krebskranken. Deutsch. med. Wohnschr., 1914, xl, 590-591.

43. Keidel, A. and Hurwitz, S.H.: A comparison of normal and syphilitic extracts by means of the Wassermann and epiphanin reactions. Jour. Am. Med. Assn., 1912, lix, 1257-1262.

44. Kelling, G.: Zur Aetiologie der bösartigen Geschwülste. Wien. med. Wohnschr., 1903, liii, 1432-1444. Quoted by Wolff, iiib, p. 557.

45. Kópinow, L.: [Resistance of mice to cancer after repeated injections of heated cancerous tissue.] Reúnion soc. belge biol., 1920, 77-79. Chem. Abstr., 1921, xv, 3319.

46. Kolmer, J.A.: Infection, immunity and specific therapy. Philadelphia, Saunders, 1917, 978 pp.

47. Koritschoner, R. and Morganstern, O.: Refraktometrische Untersuchungen über die Reaktionen zwischen isolierten Krebszellen und Blutserum (Freund-Kaminerische Reaktionen). Biochem. Ztschr., 1920, civ, 259-279.

48. Kross, I.: Effect of blood from immune animals upon transplantable tumors. Jour. Cancer Res., 1921, vi, 25-30.

49. Kross, I.: Parabiosis and tumor growth. Jour. Cancer Res., 1921, vi, 121-128.

50. Kühne, W.: Ueber die Verdauung der Eiweisstoffe durch den Pankreassaft. Arch. f. path. Anat., 1867, xxxix, 130-174.

51. Kühne, W.: Ueber das Trypsin (Enzym des Pankreas). Verhandl. d. naturh.-med. Ver zu Heidelb., 1874-1877, n.F., i, 194-198.

52. Levin, I. and VanSlyke, D.D.: Results of applying a quantitative method to the Abderhalden serum test for cancer. Jour. Am. Med. Assn., 1915, lxv, 945-946.

53. Lewin, C.: Immunisierungsung Heilversuche mit Autolysalen bei Rattentumoren. Ztschr. f. Krebsforsch., 1911-1912, xi, 317-334.

54. Lewin, C.: Die Wirkung von Schwermetallen auf die bösartigen Tiergeschwülste. Berl. klin. Wohnschr., 1913, l, 541-542.

55. von Leyden, E. and Bergell, P.: Ueber Pathogenese und über den spezifischen Abbau der Krebsgeschwülste. Deutsch. med. Wchnschr., 1907, xxxiii, 913-914. Quoted by Wolff, ii, p. 24.

56. Looper, Forestier and Tonnet: La parenté des albumines, des tumeurs et du sérum des cancereux prouvée par l'anaphylaxie. Compt. rend. Soc. de biol., 1920, lxxxiii, 1086-1088. Progrès méd., 1920, 3.s., xxxv, 355.

57. Luden, Georgine: Studies on cholesterol. IV. Experiments concerning the relation of diet, the blood cholesterol, and the "lymphoid defense". Jour. Lab. and Clin. Med., 1917-1918, iii, 141-174.

58. Lunckenbein: Zur Behandlung maligner Geschwülste. München. med. Wchnschr., 1914, lxi, 18-21. Quoted by Wolff, iiib, p. 571.

59. Macleod, J.J.R.: Physiology and biochemistry in modern medicine. 5 ed. St. Louis, Mosby, 1920, 992 pp.

60. von Monakow, P.: Beitrag zur Serodiagnostik der malignen Tumoren. München. med. Wchnschr., 1911, lviii, 2207-2211.

61. Neuberg, C.: Die Physiologie der Pentosen und der Glukuronsäure. Ergebn. d. Physiol., 1904, iii, 373-452. Quoted by Wolff, ii, p. 24.

62. Odier: Quoted by Wolff, iiib, p. 572.

63. Pesci, E.: Richerche sierologische nel cancro. Riforma med., 1920, xxxvi, 689-692.

64. Piazza: Quoted by Pesci.

65. Pick and Pribram: Quoted by Pesci.

66. Pregl, F.: Beiträge zur Methodik des Dialysierverfahrens von E. Abderhalden. Fermentforsch., 1914, i, 7-12.

67. Rabinowitch: Quoted by Pesci.

68. Robin, A.: [Nitrogen in the cancerous liver.] Bull. de l'Acad. de méd. de Par., 1919, lxxi, 799-811.

69. Robin, A.: L'azote albuminoide dans le sérum du sang cancéreux. Bull. Acad. de méd. de Par., 1920, lxxiv, 51.

70. Rohdenburg, G.L. and Pohlman, H.F.: Hyperglycemia in its relation to immunity. Am. Jour. Med. Sc., 1920, clix, 853-866.

71. Ronchèse: Quoted by Pesci.

72. Rowe, A.H.: The albumin and globulin content of humna blood serum in health, syphilis, pneumonia, and certain other infections, with the bearing of globulin on the Wassermann reaction. Arch. Int. Med., 1916, xviii, 455-473.

73. Rülf, J.: Die idioplastische Verbildung der Krebszelle und ihre Ursache mit

besonderer Berücksichtigung des proteolystischen Enzyme. Ztschr. f. Krebsforsch., 1906, iv, 417-434. Quoted by Wolff, ii, p. 24.

74. Russell, B.R.G.: The nature of resistance to the inoculation of cancer. Third Scient. Rep. Imp. Cancer. Res. Fund., 1908, 341-358. Quoted by Woglom.

75. Sajous, C.E. deM.: The internal secretions and the principles of medicine. 8 ed. Philadelphia, F. A. Davis Co., 1918, ii.

76. Sherman, H.C.: Chemistry of food and nutrition. New York, Macmillan, 1915, 355 pp.

77. Spirlas: Ueber Verdauungsvakuolen und ihre Beziehungen zu den Fea-Plimmerschen Krebsparasiten. München. med. Wohnschr., 1903, l, 825-826.

78. Stammler, A.: Quoted by Wolff, iiib, p. 571.

79. Stewart, G.N. and Rogoff, J.M.: The action of drugs upon the output of epinephrin from the adrenals. Jour. Pharmacol. and Exper. Therap., 1919, xiii, 95-166.

80. Thirloix: Quoted by MacNalty, A.S. and Malloch, A.: Influenza. Nelson's Loose-Leaf Med., 1920, i, 635.

81. Tokuda, K.: Refractometric studies with the sera of syphilitic patients under arsphenamin and neo-arsphenamin treatment. Proc. Soc. Exper. Biol. and Med., 1920-1921, xviii, 151-153.

82. Tokuda, K.: Refractometric studies in human syphilis with special reference to changes during treatment with arsphenamin and neo-arsphenamin. Arch. Dermat. and Syph., 1921, iv, 512-525.

83. Uffreduzzi, O.: Innesti di tumori e autolizzato fetale e neoplastico. Tumori, 1912-1913, ii, 393-409. Quoted by Wolff, iiib, 518; 575.

84. Vaughan, Friedberger, Weil, Doerr and Gooa: Quoted by Kolmer.

85. Vidal, E.: Recherches sur les sensibilisatrices contenues dans le sang des animaux traités par des émulsions de cancers épithéliaux. Bull. d. l'Assoc. franc. p. l'etude du cancer., 1910, iii, 81-92. Quoted by Wolff, iiib, p. 749.

86. Vidal, E.: Influence de l'état physico-chimique de l'antigène sur la teneur en sensibilisatrices du sang des animaux injectés de cancer épithélial. Bull. d. l'Assoc. franc. p. l'etude du cancer, 1910, iii, 254-267.

87. Weichardt, W.: Ueber neue Methoden der Immunitatsforschung. Berl. klin. Wohnschr., 1908, xlv, 954-955.

88. Weichardt, W.: Eine neue serologische Methode zur Syphilisdiagnose. Deutsch. med. Wohnschr., 1911, xxxvii, 154-155.

89. Werner: Quoted by Wolff, iiib, p. 566.

90. Woglom, W.H.: Studies in cancer and allied subjects. The study of experimental cancer. New York, Columbia Univ. Press, 1913.

91. Wolff, J.: Die Lehre von der Krebskrankheit, von der ältesten Zeiten bis zur Gegenwart. Jena, Gustav Fischer, Bd. i, 1907; Bd. ii, 1911; Bd. iii, 1913.

92. Wood, F.C.: A review of the advances in our knowledge and the treatment of cancer in the last thirty years. Med. Rec., 1915, lxxxviii, 1-4.

93. Zinsser, H.: Infection and resistance. New York, Macmillan, 1919, p. 538.

among 102 patients suffering from cancer in India, and Sykes (1902) reported numerous instances of gastric carcinoma among Hindus and Chinamen, whose diet is known to consist chiefly of vegetables. This shows, that the ability of the body to "handle" or metabolize its food intake properly may be of far greater importance than the composition of the diet. In malignant conditions only the systematized study of dietary measures combined with chemical analyses are likely to yield results of practical and economic value: experimental findings, which will be discussed, support this deduction. The fact, that in the United States alone one in every fourteen men and one out of every eight women succumb to malignancy (W. J. Mayo) suggests the economic value of such investigations. Unfortunately, little time has been devoted so far to the problems of nutrition in cancer research.*

The idea that there is some relation between the diet and cancer dates back to gray antiquity; it can be traced through the entire history of medicine. The weirdest, most illogical, and most repulsive dietary measures have been advocated for the benefit of the victims of malignant growth: witness, the drinking of warm goose blood, the consumption of live lizzards and the ingestion of soap emulsified in milk (Dupré de l'Isle, 1774). In the main, however, the conception centered around the harmful effects of meat and the prophylactic or curative properties of cereals and vegetables.

At the beginning of the Diathesis Period these conceptions were naturally revived, elaborated and defended with enthusiasm. Physiology, however, was still in its infancy and biochemistry practically non-existent. As the result nearly every article of food in turn was accused of furthering the development of cancer by certain physicians, only to be exonerated and extolled as beneficial by others: milk, cider, vegetable proteins, and tomatoes did not escape this fate any more than did meat, spices, oysters, and shell-fish. The arguments for or against these luckless comestibles were based either on deduction or on more or less accurate observations; but it is interesting to note that experimental data, gathered

* In the American Journal of Cancer Research 1916-1921 only two papers bearing on the relation of nutrition to tumor growth will be found.

several decades later have lent support to some of these empirical assumptions.

Beneke, (1875) whose activities and modern conceptions have already been discussed, "was the first to attempt transferring dietetic measures in malignancy from a purely empirical to a more scientific basis" (Wolff). Beneke's conviction that malignant proliferation was connected with an inadequate oxidation of protein resulting in the retention of phosphates and albuminates, and his observation that cancer is extremely rare among the inmates of prisons (where the diet is necessarily restricted) led him to advocate a special menu for patients after operation. He did not believe that cancer could be actually prevented by the composition of the diet, but he considered that in facilitating the chemical tasks of the organism the incidence of recurrence might be reduced. The diet which he suggested included two ounces of meat daily, soups made without meat, twice or thrice baked bread in preference to ordinary bread, a plentiful supply of fruit and green vegetables and a considerable intake of liquids in the form of tea, coffee, and light wines; beer was only to be allowed in small quantities. A similar type of diet was recommended by Esmarch, who combined it with the internal administration of arsenic (1878), by Van den Corput in Belgium, who looked upon integrity of the liver functions as essential to the prevention of recurrence (1883), by Verneuil, who defended restriction of the food intake, especially of meat, at the Surgeon's Congress in Paris (1900), by Hochenegg in Vienna (1911) and by Sternberg, who even attributed diagnostic significance to a pronounced dislike of meat in patients in whom no conclusive evidence of malignancy could be found (1911). In recent years (1914-1921) the advantages of the dietary management of malignant conditions have been emphasized repeatedly by Bulkley, but the unfortunate vehemence with which he denounced simultaneously both surgical treatment and radiotherapy is more likely to have prejudiced the medical profession against dietary measures than to have carried conviction.

Because of their historical interest, and since it is the object of this publication to correlate as far as possible former theories and recent findings, the controversies which centered around certain ingredients of the diet will be considered: chief among these ingredients are salt (sodium chlorid) proteins and vitamins.

Braithwaite by his so-called salt theory (1902) introduced - one might say almost unwittingly - a new series of problems into cancer research: namely, the problems connected with the balance of inorganic salts in the body. Initially this theory was not based on any such scientific premises; it was founded on a collection of heterogeneous observations and questionable deductions. This is by no means surprising for biochemistry had not yet become an integral part of medicine; Albu and Neuberg's "Mineral Stoffwechsel" was only published in 1906, the first edition of Hawk's "Practical physiologic chemistry" appeared in 1907, and simple clinical methods for the determination of chlorids in blood and urine were either unknown or little used.*

The fact that the consumption of meat in England, and with it the consumption of salt, had increased four-fold during the past fifty years led Braithwaite to assume that an excessive salt intake "by augmenting tissue irritability contributed directly to the increase of cancer" (Wolff). He pointed out that neither savages nor wild animals suffer from malignancy, because their diet is not seasoned artificially, adding that the only known instance of cancer in a rhinoceros had been traced to the animal having been given salt. The high death rate from cancer among sailors (60:1000) was referable, according to Braithwaite, to the amount of salt meat consumed aboard ships; uterine cancer was practically unknown among Jewish women because they ate neither ham nor bacon; hypochlorhydria in gastric carcinoma resulted from the reabsorption of all the available chlorids

* Vollhardt's determination for chlorids was known in 1874, and Arnold's modification in 1880; both methods were complicated and only meant for urinalysis. The Harvey-Vollhardt method was published in 1910, the McLean-van Slyke method for blood and urine (1915) was accurate but by no means simple. A simplified method was published in 1920 by Meyers and Short, who mention "that the estimation of chlorids has not received more clinical attention must be ascribed either to lack of appreciation of the possible value of the test or to difficulties of the tech-

by the cancer cells; and the cachexia of malignancy was caused by the increased sodium chlorid content of the blood. Quaint as these assertions may sound today, barely twenty years later, they gave rise to considerable discussion. Stricker (1903) replied to Braithwaite's arguments by pointing out that there is no striking increase of the cancer incidence among people who live near the sea nor among the workers in salt mines who consume a great deal of salt, while sheep which need an ounce of salt daily to remain in good condition never develop cancer. Bougard in Belgium, whose entire life was devoted to cancer research and whose book "Etudes sur le cancer" (1882) is called a valuable contribution by Wolff, expressed the opinion that the intake of salt was beneficial rather than harmful; the experiments of Moraczewski (1895) suggested that administration of sodium chlorid and calcium phosphates caused a reduction of the protein disintegration, inhibiting necrosis. Ross of Simla (1903) even claimed to have cured cancer by the administration of large amounts of salt; he attributed these results to the effect of chlorin on the saccharomyces, which were at this time considered to be the cause of cancer (Wolff). The controversy appears to have died a natural death, neither the opponents nor the defenders of sodium chlorid being in a position to substantiate their arguments by conclusive evidence.

It should be mentioned here that von Fürth in his "Chemistry of metabolism" (1916) speaks of "the remarkable 'salt-and sugar-fever', which has recently received much consideration but which is as yet without explanation, a temperature exaggeration which has been noted in animals and human beings (especially in infants, but also in adults) after intravenous, subcutaneous, oral and rectal introduction of solutions of sodium chlorid or of sugar, and which is apparently accompanied by an increased production of heat and increased protein metabolism". The question presents itself if the improvement of malignant conditions

nique". Whitehorn's modification of the Vollhardt method (1921) is simple, allows the use of the protein-free filtrates described by Folin and Wu and furnishes "a sharp end-point" for the color reaction in titration. (Jour. Biol. Chem., 1920-1921, xlv, 449-460).

mentioned by Bougard might be connected with this type of fever: the activation of metabolism by bacterial infections (erysipelas) and by Coley's treatment is known to have beneficial effects. However, in this instance as in many others the "individual chemistry of the host" will doubtless prove to be the deciding factor; for neither erysipelas, Coley's treatment, nor for that matter any kind of therapeutic measure, which has given good results in a great number of cases, has invariably proved successful in all.

The relation of the food intake to the balance of inorganic salts in malignancy has been specially emphasized by Forbes Ross in his book "Cancer: the problem of its genesis and treatment" (1912). The conclusion which he reaches is that the potassium deficit which characterized the diet of modern civilisation may be an important factor in the development of malignant growth. Although certain hypotheses presented in the first chapters (III-V), concerning the "conjugation or amalgamation" of leucocytes with fixed tissue cells seem far-fetched and untenable, the following chapters contain many considerations that are valuable and well worth reading carefully. The author states that he is "writing as a surgeon" and points out that his suggestions with regard to the use of "the assimilable salts of potassium, such as neutral citrate, tartate, phosphate, bicarbonate and hypophosphite" (he excludes potassium iodid and chlorate) are based on fifteen years' experience, during which close attention was paid to microscopic diagnoses, and that the treatment which he recommends is "quite compatible with any reasonable and rational medical or surgical treatment extant". He says "It is better to remove the primary focus by surgical operation than to let it remain as a source of possible future renewal of the disease", but that he has found that administration of potassium salts in combination with (but even without) radium or roentgen-ray treatment caused distant glandular involvement, secondary nodules, and recurrences to regress and disappear in a surprising manner. Although potassium in excessive dosage may affect the heart, it has been his experience that smaller doses have a beneficial influence on the heart action. This is fully corroborated by Bastedo (1915) and by Cushny, who says: "The poisonous action of potassium on the heart has given rise to exaggerated apprehensions of the danger of using its salts in therapeutics, and it may, therefore, be noted that potassium has no effect on the heart when given by the stomach . . .". While all the details to which Forbes Ross calls attention cannot be discussed here it would seem that a thorough investigation, by means of modern biochemical methods, of the observations which he made might prove of great value in cancer research.*

Robin of Paris began to study the balance of inorganic salts in malignancy as early as 1907. He refers to his previous (1914) investigations in a recent publication (1921) in which he states that cancerous tissues fix an excess ("se sur-minéralisent") of chlorids, sodium and potassium, while showing a deficit ("se déminéralisent") with regard to calcium and iron. Robin, therefore, looks on chlorin, sodium, and potassium as "constructive agents" in neoplastic growth, but on silicon, calcium, magnesium, and phosphorus as "defensive agents", impeding proliferation. His last study contains the following observations: to three patients, who were fifty, forty, and sixty-five years old, and of whom the first had a cancer of the colon, the second a cancer of the esophagus, and the third a primary carcinoma of the liver (all presumably inoperable) fairly large doses of calcium glycerophosphate, magnesia, and sodium silicate were given three times daily for periods of four, three, and two months. At necropsy histologic examination revealed a marked preponderance of connective tissue in all the tumors. Chemical analyses of the tumor tissues for total nitrogen, calcium, magnesium, and silicon showed an excess of the mineral salts as compared with the tumors of patients who had not received this medical treatment: although the total average nitrogen

* Recently attention has been called to the value of potassium therapy in a pamphlet issued by the National Biochemical Laboratory (Therapeutic Leaves) with the collaboration of E. P. Robinson, M.D. The preparation recommended is called "Tokarkim", but the commercial character of this publication is scarcely likely to further the recognition of the therapeutic principles connected with potassium therapy.

values were the same. Both mineral salts and total nitrogen proved to be much higher in cancerous than in normal liver tissue. The increase of the mineral salts was greatest for silicon, somewhat less marked for calcium, and smallest for magnesium. The excess of silicon was greatest in the case of the patient to whom the mineral salts had been administered for the longest period and whose tumor showed the most striking increase of connective tissue. Robin concludes that the therapeutic administration of silicates may therefore be looked on as a means of furthering the production of connective tissue, "by supplying the material necessary for its formation", since, according to our present knowledge of biologic processes, connective tissue "is one of the spontaneous defence-reactions of the organism against malignant growth".

In the Seventh Scientific Report of the Imperial Cancer Research Fund (1921) very valuable data on the action of calcium and sodium ions in malignant growth are reported by Cramer. These data are part of a long series of investigations "on the biochemical mechanism of growth" by Cramer (1908, 1910, 1916), by Cramer and Pringle (1910) and by Cramer and Bullock(1913). In Cramer's recent experiment emulsified portions of a tumor strain, "No. 63 of the Imperial Cancer Research Fund, which grows evenly and in a high percentage (90-100 per cent) of inoculated animals" were exposed in vitro before inoculation to the action of equimolecular solutions (M 7.5) of calcium and sodium chlorid. The cells which had been suspended in calcium chlorid showed a distinct, but transient inhibition of growth; they apparently recovered about two weeks after transplantation and their recovery could be hastened by re-inoculation into "fresh mice", but the growth of the tumors was markedly reduced and delayed as compared with the controls. Suspension in sodium chlorid did not cause any inhibition of growth, possibly even a slight acceleration. The inhibiting effect of the calcium solution could be counteracted by subsequent suspension in sodium chlorid, but it could not be intensified by removing the tumor and by again submitting the cells to the action of the calcium ions before the second inoculation; in fact, cells which had been subjected to this manipulation five times (or "through five generations" as Cramer expresses it) showed exactly the same degree of inhibition as cells which had only been suspended in the calcium chlorid solution once. That neither the mechanical manipulations, damaging the vitality of the cells, nor the actual number of cells inoculated were responsible for the temporary inhibition of growth by calcium chlorid was proved by the following facts: the cells subjected to both calcium and sodium treatment and, therefore, exposed to longer manipulation did not grow less well than the controls; calcium series showed a marked inhibition of growth even when transplanted in doses of 0.13 c.c. as compared with control series in doses of only 0.01 c.c. Both histologically and chemically "a distinct difference" could be noticed in the cells after treatment with the various salt solutions; after suspension in calcium chlorid solution "the protoplasm appears denser and less spongy than that of cells treated with sodium chlorid solution or cells which have received no treatment at all". The dense protoplasm of cells treated with calcium chlorid solution "becomes looser again when these cells are treated subsequently with sodium chlorid solution". Chemical analyses revealed that the reduction of the water content of the protoplasm by calcium salts was completely counteracted by the sodium salt.

Cramer suggests that "the greater water content of rapidly growing cells is due to the greater inhibition of the protoplasmatic colloids"; that "it should be possible to alter the rate of growth by altering the inhibition of the protoplasmatic colloids"; hence, "the experiment affords an insight into the nature of the processes which lead to a temporary diminution of the vitality of cancerous cells." In this connection he recalls that there are fluctuations in the rate of growth of tumor strains and that "during such a period of depression a tumor strain may even die out". His conclusion is, therefore: "This cyclical period which is conditioned by factors inherent in the cell indicates that the cancerous cell is subject to senescence and in that respect resembles the normal cell, but that it differs from the latter in being able to rejuvenate itself spontaneously and thus escape death".

Cramer attributes the fluctuation of growth to "factors inherent in the cell": this deduction seems open to question. His experiment proves that the medium into which they are put affects the cells; the investigations of Loeb on the development of sea-urchins show that differentiation is profoundly influenced by the surrounding medium. The vitality of any cancer strain can only be ascertained by the number of successful inoculations and the size of the tumors furnished by a given strain. The periods of depression of growth themselves have been revealed by the results of inoculation. The question is therefore justified: "Is the cyclic depression really conditioned by factors inherent in the cell, or do those factors reside within the animal used for inoculation?" The latter assumption seems nearer the truth. Fluctuations are known to occur in all "living" organisms, both in health and in disease: the periodicity of menstruation, and of the breeding time of animals, the cyclic manifestations of hyper-thyroidism and of gastric and duodenal ulcer (spring and autumn "attacks") need only be recalled. Kendall found that a far greater yield of thyroxin could be obtained from the thyroids of hogs killed during the summer, than from those of animals slaughtered in winter. The effect of the thyroid on metabolism needs no comment. The connection between pregnancy, alterations of metabolism, and the functions of several glands of internal secretion is admitted: Slye proved that the growth of spontaneous tumors in mice could be temporarily retarded by intercurrent pregnancies.

In view of all of these facts the cyclic changes in the metabolism of the animals used for inoculation are far more likely to influence the rate of growth of tumors than factors inherent in the cell. This point of view has received but little consideration; its oversight is likely to have hindered, its recognition will doubtless further the progress of cancer research. For, if short and transient suspension in calcium salt solutions produces marked inhibition of growth, which can be antagonized by the influence of sodium, how much greater must the effects of these salts be when cells are exposed to them for long periods and in constant contact with them, as happens through the intimate connection of a tumor and its "host". Cramer mentions that calcium treated cells "recover" more rapidly when transplanted into "fresh mice". It is obvious, moreover, that the progress of malignancy in human sufferers will be similarly influenced by the balance of inorganic salts, which is in its turn regulated by many organs. That lesions or the congenital inferiority of any of these organs will lessen the chances of the victim will be readily conceded: the regulation of the calcium metabolism by the parathyroid glands might be mentioned as an illustration. Thus, the admirable investigations of Cramer and his collaborators not only furnish an insight into the biochemical mechanism of growth, they may, studied from a wider point of view than that which embraces the cell alone, verily "serve as a guide in an attempt to find a rational therapeutic of cancer" (Cramer).

So far clinical researches concerning the balance of the inorganic salts in malignant disease have not yet furnished the information that was expected of them. The reasons for this are manifold. The technical difficulties, and the very recent acquisition of suitable methods have already been discussed. Investigations have been restricted to a relatively small number of patients; the investigators have had to be satisfied with one, or at the best, a few tests on each patient as the result of circumstances beyond their control; whereas serial investigations alone are capable of furnishing definite information. The apparently normal findings obtained under such conditions in malignancy were little calculated to arouse enthusiasm for work along these lines. The far more definite findings, with regard to the chlorids, especially in nephritis and the possibility of nephritic complications in malignant disease naturally led to restriction of the study of chlorid metabolism to renal disorders. There is another factor to which Pruche has called attention after he studied the blood chlorids in a great number of volunteers at the Naval Academy of Brest (France), and which explains the prevalence of negative findings even in disease. Pruche found, namely, that the body apparently endeavors to maintain the isotonic quality of the blood at all costs: an increase of the water intake or a saltless diet, which would tend to transform the blood into a "hypotonic salt solution" immediately calls forth a retention of chlorids, possibly even a mobilization of the salt reserves; whereas the increased consumption of sodium chlorid is promptly antagonized by a mobilization of water from the tissues to prevent "hypertonicity" of the blood serum. Consequently the blood chlorids show little or no variations, unless the regulating mechanism is very severely damaged. Pruche, therefore, distinguishes between a physiologic and a pathologic retention of chlorids. In a healthy person on a salt-free diet physiologic retention occurs because the sodium salts ought to be retained; pathologic retention only occurs when the body has lost the power of eliminating the salts. A simple method for differential diagnosis between these two types of retention with the aid of the blood alone (no urinalysis being required) has been devised by Pruche; the method is based on the relation of the sodium chlorid content of the blood to the dry residue of the same sample. The procedure is as follows:* The sodium chlorid content of a blood sample is determined by chemical analysis; Pruche uses a new modification of the Vollhardt method, but his "normal" values ranging from 5.6 to 5.9 gm. for each liter are in perfect harmony with the average normal value 0.5885 gm. for each 100 c.c. given by Whitehorn, so that the Whitehorn modification could also be used. The total dry residue of a known volume of the same sample after thorough desiccation is determined by weighing on an analytic balance. The relation between the sodium chlorid content and the dry residue minus the values found for the sodium chlorid content is determined by simple division according to the formula $\frac{\text{sodium chlorid values found by analysis}}{\text{weight of dry residue minus sodium chlorid values}}$, which Pruche calls "formule hematologique de la rétention chlorurée". The result-

* The procedure is given in detail because its description is somewhat complicated

ing quotient ("coefficient rénal d'excrétion des chlorures") is practically constant in health ranging from 0.06 to 0.07. A quotient which is above 0.07 indicates a pathologic salt retention; a quotient below 0.06 shows that an insufficient amount of chlorids is being retained with resulting tendency to demineralisation of the body. The importance of Pruche's observations needs no comment. The unsatisfactory results of chlorid determinations in many diseases is thus fully accounted for as well as the negative findings in malignancy reported by several observers (Robin, Horst, v. Müller, Laudenheimer, Meyers and Rieger). Since the kidneys deserve the title of "the scullery maids of metabolism" and suffer by being over-worked and damaged proportionately to the amount of undesirable substances, including metabolites, that have to be eliminated, the relative frequency of renal involvement in malignancy is by no means surprising and occurrence of demonstrable retention of chlorids in severe kidney lesions alone an inevitable phenomenon. In fever, in decompensation of the heart, in anemia or cachexia chlorid retention may, or may not be caused entirely by temporary or relative renal insufficiency; it may also be the indirect result of more deeply seated metabolic disturbances; for Horst mentions that in a case of "renal uremia" the sodium chlorid blood values were normal (0.44 per cent by Bang's micro method); whereas in a case of "eclamptic uremia" the values were exceedingly high (0.99 per cent); yet both patients were comatose at the time. Massaglia's experiments (1921) prove conclusively that by damaging the parathyroids the clinical as well as the histologic picture of eclampsia can be produced in animals, but that injury of the liver (by phosphorus), or of the kidneys (ligation of ureters or blood vessels) alone are incapable of producing these results.

The deficiency of calcium salts in the modern diet has been the object of much discussion, as an editorial in the Journal of the American Medical Association shows (1920). The studies of Denis and Minot indicate, however, that ingestion even of ninety grains of calcium lactate daily for five days does not

in the original articles, and is not given in the abstracts.

greatly alter the calcium concentration of the blood, unless it happens to be low; yet the beneficial effects of calcium salts in postoperative tetany are well known, and the empirical administration of calcium lactate to combat the muscular spasms and the shivering fits caused by chronic carbon monoxid poisoning gave satisfactory results (Laden). It seems probable, therefore, that, if the alterations of calcium metabolism were studied by some procedure similar to that recommended by Pruche for the chlorids, valuable data might be brought to light.

Extensive investigations of the sodium and calcium metabolism in malignancy according to Pruche's methods might help to explain the observations of Cramer and the findings of Robin, and would doubtless further the progress of cancer research.

The protein content of the diet. - No article of food has been accused more emphatically, everywhere and at all times, of causing or promoting cancer than meat. During the earlier decades of the diasthesis period, before Kossel studied the components of the protein molecule, the "building stones" as he first called them (1895-1898), meat and protein were looked on as practically synonymous terms. True, Braconnet had isolated the simplest protein, glycin, by hydrolysis as early as 1820; Heller's test for albumin and Millon's reagent were devised in 1844. But Liebig (1803-1873), though he discovered tyrosin and glycocoll (1846-1849) believed that there is "only one aboriginal protein" (Garrison). He was the first to use the term metabolism (Stoffwechsel) in his book "Organic chemistry and its application to physiology and pathology". Yet, the scientific obstinacy which characterised him made him say to Lord Kelvin that he would "more readily believe that a book on chemistry or botany could grow out of dead matter by chemical processes, than that a leaf or a flower could be influenced in its growth by chemical forces". He even refused to believe that yeast was alive and he "declined to look through a microscope" (Garrison). Günsburg, however, whose name is associated with the test for free hydrochloric acid in analysis of the gastric content, already pointed out

(1853) that both cancer and obesity might result from an excess of vegetable diet. Physiology made rapid strides between 1850 and 1890. The problems of digestion and nutrition, revealed by the pioneer work of Beaumont on an accidental gastric fistula in the Canadian half-breed, Alexis St. Martin (1825) were beginning to be solved by the investigations of Claude Bernard (1813-1878) on the glycogenic function of the liver, the action of the pancreatic juice and the "preparatory" character of gastric digestion, by the studies of Bitter and Schmidt (1852), of Pavlow, Voit and Pettenkofer (1861-1881). Kjeldahl's method for determination of the nitrogenous products of metabolism was published in 1883. Cancer research and physiologic chemistry, however, remained strangers to each other until the beginning of the twentieth century. As the result, the physiologic effects of protein intake on malignant growth received little attention; endless arguments as well as statistical researches were used chiefly to establish the relationship between the cancer incidence and the consumption of meat.

<u>Haviland's theory</u> (1875-1892). That the geological formation of the soil, hills or valleys, rocks or marshes, controlled the cancer rate was met by Pickering and others by the argument that the inhabitants of the highlands are usually poorer than those of the plains and, therefore, consume less meat. Rous (1893) considered the consumption of pork a predisposing factor in cancer; Bauby argued that the population of Toulouse, where pork is the staple food, does not show a higher cancer incidence than the Jews who abominate pork (French Congress of Surgeons 1894); Sawyer (1900) blamed the consumption of raw meat. Sherrett (1907) was the first to consider the effect of the nucleins and nucleic acid in cancer, although the influence of these protein derivatives on gout had long been established and a relation between gout and cancer had often been suggested (Récamier, 1829; Basin, 1858; Romain Vigouroux, 1906). Williams, in his comprehensive work "The natural history of cancer" (1908) expressed the conviction: "Ascertained facts justify the belief that there is a certain relation between conditions of

nutrition and the incidence of cancer growth".

It may be of interest in this connection to point out that recent investigations are tending to support the old, strictly deductive theories. Changes in the morphology of the polymorphonuclear leucocytes, similar to those found in the blood of patients suffering from carcinoma, have been produced by Gruner in his own blood by experimental ingestion of a great deal of pork (1916); these findings were duplicated by Luden (1917) as the result of an experimental all-meat diet and were found to be accompanied by marked changes in the blood cholesterol values. Gröbly, Kocher's assistant, in a paper supervised by Abderhalden and published in the Kocher Memorial number of the Archiv für klinische Chirurgie (1921) has presented evidence that the nucleoproteins are predominantly important in cell growth and that disturbances of nucleoprotein metabolism predispose to malignant disease. The studies of Killian and Kast (1921) on the significant chemical changes in the blood coincident with malignant tumors in 119 cases have revealed a great preponderance (80 per cent) of high and increased uric acid values: that is, findings similar to those observed in gout, "A metabolic disease of uncertain origin . . . almost uniformly associated with an increased amount of uric acid in the blood" (Da Costa, 1919).

It is only during the last decade that the truth of the statement "The cancer problem is but one aspect of the broader problem of growth" (Benedict and Rahe, 1917) has begun to be fully appreciated. Nutrition and growth, however, have been an object of investigation for more than twenty years and the literature on metabolism has assumed gigantic proportions. The retardation of tumor growth by starvation of the host was already known to the Romans and made use of by them in the so-called "fames cura" (hunger treatment), a therapeutic measure which was resorted to and extolled intermittently during the following centuries. Moreschi (1909) was the first to test the value of starvation by animal experiment; his findings were corroborated on the whole by Rous (1914) and since then the dictum, "Starve your mouse and you will starve its tumor" has been proved correct by innumerable experiments. The conception of cancer as a disease of over-nutrition is supported, moreover, by recent observations; although inadequate combustion of the food may prove to be a more important factor than its excessive intake. The statistics of the department of public health in Edinburgh show that the smallest number of deaths from cancer occurred in the houses with the lowest rental, while the highest cancer incidence was found where the rental was "indicative of the prosperous and well-to-do" (Hoffman, 1916); phthisis, on the other hand was proclaimed the disease of poverty by the same statistics. Evidence derived from the results of the Medico-Actuarial Investigation also proved, "Cancer is more common among overweights than among underweights". (Hoffman, 1917).

The effect of divers types of protein on nutrition and growth were first studied by Sweet, Corson-White and Saxon (1913), but Hopkins, Osborne and Mendel, Lusk, McCollum, and a host of other workers in America and in Europe have contributed in a brilliant manner to our knowledge of the biologic values of food. It was found, for example, that proteins can be broken up into about twenty different compounds (amino-acids) and that all proteins, whatever their origin, contain some of these compounds, but in greatly varying proportions. A given protein may lack one or more amino-acids, with the result that its "protein value" disappears altogether. A young animal dies when zein, a protein contained in corn, is the sole protein constituent of its diet, even though the diet be adequate in other respects; for zein does not contain the indispensible amino-acids lysine and tryptophane. If tryptophane alone is added to the diet the animal will maintain its body weight, though it will fail to grow; if, however, both lysine and tryptophane are added, a normal growth curve will be obtained. "The problem of protein requirement is thus resolved into a problem of amino-acid requirement, limited on the one hand by the body's needs and on the other hand by its ability to construct amino-acids itself" (Pettibone, 1917). In malignant growth a third limitation of the body's activities may have to be considered: not only the proper utilization or the synthesis of amino acids but the adequate elimination of undesirable and harmful products of protein disintegration. That any atypical cleavage of the protein molecule will complicate the tasks of the body still further and render elimination of metabolites more difficult, is self-evident. Killian and Kast have pointed out that the increase of uric acid in the blood coincident with malignant tumors is not caused by the reabsorption of tumor proteins, since the chemical findings often remain unchanged after the tumor has been removed; nor is the degree of renal impairment which it reveals dependent on the age of the patient. The conclusion that this uric acid retention is indicative chiefly of renal involvement does not seem to do full justice to the significance of the observations, however, as will be discussed in detail in connection with the chemistry of the blood in malignant disease.

The foregoing brief historical survey may suffice to show how the time-honored controversy about the effect of the meat intake on cancer has become linked, through the progress of science, not only with the problems of protein requirement, but also with the far greater problems of amino-acid and purin metabolism.

The vitamin content of the diet and other important factors. Vitamins, those "food substances of unknown chemical nature" as Palmer (1921) still calls them, became known through the investigations of Eijkman (1897). The polyneuritic syndrome of berri-berri was produced in chickens by Eijkman through prolonged feeding with polished rice. The importance of these, apparently indispensible, food accessories was only realised about fifteen years later when the term "vitamines" was introduced by Funk (1912); but many of the problems connected with the vitamin requirements of the organism are still unsolved today. Three different kinds of vitamins are known to exist, however; a "fat-soluble A" vitamin, a "water-soluble B", and a "water- soluble C", which is not universally recognised; but none of these has been isolated chemically.

The fat-soluble A vitamin is thought to be nitrogen-free; it is known to be contained in considerable amounts in dairy butter, milk, and green vegetables. Its lack often produces xeropthalmia or keratomalacia, an inflammatory condition of the eyeball resulting in blindness; but it does not always cause this disease as the recent experiments of Walker (1922) prove. Walker believes, therefore, that "hereditary disposition" may account for the "anomalous and erratic manifestations, which he observed.

The water-soluble B is looked on as "growth-promoting". Dunham (1921) introduced a "vitamin unit" for the purpose of grading the B vitamin content of vegetables; he found that potatoes, spinach, carrots, peas, and turnips contain (in the order of their sequence) from fifteen to nine units, but yeast as many as twenty units. Milk contains the A as well as the B vitamin. The relation of a vitamin deficit to diseases such as scurvy, pellagra, and rickets is still a matter of dispute, but it has been established that berri-berri is caused by lack of the water-soluble B. Goldberger showed that a diet must be low in protein and calcium as well as in the fat-soluble A to produce pellagra and Shipley, Park, McCollum and Simmonds (1921) proved experimentally that lack of the A vitamin does not cause rickets if the diet contains an adequate amount of "phosphate ion".

The work of McCarrison on "deficiency diseases" (1921-1922) furnishes evidence that Walker's "hereditary predisposition" must be closely associated with the hereditary transmission of endocrine glands which can, or cannot, respond to the emergency demands created by an ill-balanced diet. McCarrison suggests that there even seems to exist a "special relation" of the essential food ingredients to each other: "as for instance that of iodin to fats, that of vitamin B to carbohydrates, that of vitamin A to lipoids, calcium and phosphorus holding substances, and that of vitamin C to inorganic salts". The influence of the thyroid on the management of iodin compounds; of the pancreas on carbohydrates; of the adrenal cortex on the lipoids, and of the parathyroids on calcium metabolism has been established and needs no comment. McCarrison also made the observation: "Ten out of twelve young adult men developed paralysis of the lower limbs due to lathyrism - a rare malady resulting from the disproportionate use in the food of the vetch Lathyrus sativus . . . while the female members of the settlement (of natives in the Himalayas) were unaffected". He found that male pigeons develop polyneuritis more rapidly than females when fed on polished rice. His carefully controlled experiments on wild monkeys proved that a vitamin deficit caused the adrenals and pituitary to hypertrophy, although a tendency to atrophy predominated in other organs, whereas the kidneys as a rule showed little or no change. The latter observation is in striking contrast to the early disturbance of renal function in malignancy reported by Killian and Kast;* it suggests that far profounder metabolic anomalies must be present for the production of malignant disease than those produced by an inadequate diet alone. The extensive investigations of Slye on the incidence and inheritability of spontaneous tumors in mice tend to support this deduction. Because of their definite bearing on the relation of nutrition to malignant growth and on dietary experiments with tumor-bearing animals.

<u>Slye's investigations</u> have been carried on for more than twelve years; the published reports of her studies on heredity number no less than sixteen, covering a period of nearly ten years (1913-1922).** All the mice used in her laboratory have been allowed to live as long as ever they pleased; "Every effort is made to keep them alive as long as possible" (Slye), by guarding against infectious diseases and by scrupulous attention to matters of health and hygiene. Slye's mice may be said to be living under "ideal condition", even from the point of view of a mouse, if restriction of personal liberty by a cage be left out of account. The results obtained in Slye's work have been secured by the process of selective breeding alone; "The tumors are all spontaneous arising without any interference except selective breeding . . . the material used for this study are individuals

* see pages 125 and 128.
**The April number of the Journal of Cancer Research (1921) could only be published January, 1922, as the result of disturbed conditions in the printing trade.

analysed as to their hereditary potentiality" (Slye).

The term "analysis of hereditary potentiality" may require a word of explanation. It simply means this: every mouse in Slye's stock has a "Genealogical tree", such as no royal family can boast of; all its ancestors, mates, and numerous descendants as well as the marital relations of the latter, have been recorded and the data include details concerning diseases and necropsy findings. In other words, the family history of any of these mice is more complete than that of the Bourbons, the Stuarts, the Hapsburgs, or the Romanows. Some families or strains have been in Slye's laboratory for twelve years (16th report) and the word "strain" in all of Slye's publications denotes "A family arising from a mating between two definite, known individuals of known ancestry and known cause of death" (Slye).

In order to obtain a clear conception of the number of generations which a strain of mice, kept under observation for twelve years, represents, the following data may be helpful. The average span of life of a mouse is about two years, often less. Although there are mice in Slye's stock which have reached the venerable age of four and a half years or 1460 days (female 25911, mentioned in the fifteenth communication as an extensive gastric carcinoma was found at necropsy), such longevity is the exception rather than the rule and a mouse 669 days old is "an old mouse". At the age of two months a mouse may be the mother of a family, possibly even earlier; if her descendants breed at the same age she will be a great-grandmother at the end of six months. Therefore, one half year represents three generations of "mouse life". It is usually assumed that a century represents three generations of "human life". Hence, to obtain a human family history comparable to that of a strain of mice kept under observation for twelve years, an uninterrupted record covering a period of 2400 years would be needed. Such a family history would begin 400 B.C. and should contain every detail (including necropsy findings) of all the descendants of, for example, some contemporary of

Alexander the Great, or of one of those Athenian youths who wept at the death-bed of Socrates (399 B.C.).

The investigations of Slye, based on many records corresponding to family histories extending over 2400 years, have proved conclusively that (1) malignancy develops in strict accordance with the Mendelian laws of heredity; (2) malignancy is a recessive and not a dominant characteristic, because it can be bred out or "segregated out" of a given strain by selective breeding, that is, by mating generations of individuals of a known tumor-bearing strain with individuals of a proved tumor-free strain; (3) "inbreeding" does not increase the number of tumors in any strain, but eliminates malignancy by putting an end to the strain; because consistent inbreeding finally renders the offspring unreproductive, so that the strain simply dies out; (4) in any given strain, the metastatic tumors (if there are any, for "in 29,000 necropsies furnishing something over 4000 primary spontaneous tumors, mostly malignant, only 19 per cent of the tumors have metastasised") tend to occur in exactly the same organs in which the primary tumors of that strain occur; and (5) "the thing which is transmitted in the heredity of cancer is the tendency of a given organ to yield to cancer" (Slye).

The bearing of Slye's work on problems such as the production of malignant disease by dietary measures may be seen in her discussion of a paper presented at the annual meeting of the American Association for Cancer Research (1921, Cleveland) during which she made the following statement: "It might interest Dr. Bulkley and the Association to know that there is a standard diet maintained in my laboratory, which is identical for tumor and non-tumor strains. With autopsies at 29,000 and living inhabitants numbering about 13,000, all fed on exactly the same diet, the tumor strains have yielded over 4000 spontaneous tumors, while the non-tumor strains have never yielded a single tumor. No meat is ever used in our laboratory".

The bearing of Slye's work on experiments with animals in cancer research is shown by certain facts to which she calls attention in her sixteenth report, namely: (1) "The biologic difference between spontaneous and grafted tumors is so fundamental and complete, that the behavior of grafted tumors has practically no bearing upon the behavior of spontaneous tumors;" (2) "groups of mice even when purchased from one dealer are mixed lots, secured from many divergent sources, and wholly unanalysed as to their tumor potentiality;" and (3) "until stocks of animals to be used in such experiments* have been thoroughly tested out as to their inherited potentialities, such experiments are lacking in adequate control, as the factor of heredity is not being considered, although it is tremendously potent. Heredity alone would be sufficient to give the exact results attained in countless experiments, which have been conducted without any effort to study or control the heredity factor".

In the foregoing statements there are several points which deserve especially careful consideration, because they are of vital importance to the progress of cancer research and the solution of the cancer problem. These points are:

1. Biology and chemistry are so closely related as to be twin-sciences. It is impossible to conceive of "life" without chemical reactions of some sort. With the cessation of certain chemical reactions life itself becomes extinct and this is true of the simplest as well as of the most highly differentiated forms of life - of the ameba, the plant, and the vertebrate mammal. Biology, therefore, simply records indirectly the manifestations of those countless and intricate chemical reactions upon which life depends.

2. The mechanisms of biologic manifestations is most likely to be revealed by chemical investigation and knowledge of this mechanism is essential to rational therapy. If locating the enemy is the first requirement for effective strategic maneuvers, information concerning the biologic and biochemical basis of

* Slye is referring here to experiments dealing with the effect of massage and of other manipulations on the increase of metastatic tumors; but the same applies of course to other experimental procedures, including dietary measures.

disease is no less necessary for effective therapeutics; albeit that the discovery of the cure accidentally preceded exact knowledge of the nature of the disease in some instances.

3. The biologic aspects of malignancy, revealed by Slye's study of spontaneous tumors, are of paramount importance, because in man none other than spontaneous tumors occur. If it be accepted that invasive growth, resulting cachexia, and the histologic structure of tumors are criteria of the fundamental similarity of tumor growth in animals and in man, the spontaneous development of malignancy should be considered equally significant.

4. The importance of the heredity factor in the development of malignant growth can no longer be questioned, if it be recalled that by selective breeding alone Slye has produced "in two small strains (338 branch V, A and 465), derived from identical original ancestry, ten primary and five secondary liver tumors", and close on a hundred liver tumors in various strains of her stock, whereas in the immense literature on cancer in mice "there is just one mouse liver tumor on record, a primary tumor of the liver, reported by the Imperial Cancer Research Fund of England". The extreme rarity of tumors of the liver in mice is ample guarantee that no such tumors have been overlooked at necropsies: any research worker who happened to find one, would have hastened to publish the event. Facts, therefore, fully justify Slye's conclusion: "The tissues of these organs are of the same nature as the ancestral tissues from which they are derived. There is a specificity of tissue type from liver to liver, from kidney to kidney, etc., which will make those organs react in a given way to a given type of irritation".

5. This specificity of tissue type, transmitted according to the laws of heredity, determines not only how an organ will react to a given kind of irritation, it also determines to what extent and in what manner the organ will be able to perform its chemical tasks. If hereditary inferiority causes an organ to do its chemical work in a half-hearted, slipshod way, severe chemical disturbances

affecting the body as a whole will result. Such chemical or metabolic disturbances, moreover, are likely to become a source of perpetual irritation, the source of their production being ever present: they will disturb congenitally inferior or accidentally damaged tissues in proportion to the inherent weakness of such tissues, although the degree of irritation produced might not be resented by normal tissues living under normal conditions. A simple illustration will show the truth of this inference. If a moderately large amount of sugar be consumed by a healthy person, no harm will result: the fluctuations in the concentration of the blood sugar will be transient and within normal range. If the same amount of sugar be given to a diabetic with a congenitally inferior or accidentally damaged pancreas, severe metabolic disturbances will be produced and the patient may even be precipitated into fatal coma.

In a paragraph dealing with the influence of the diet on malignancy a discussion of the heredity factor and of the intimate relation between biology and chemistry may or may not seem a digression, according to the reader's point of view. It is impossible, however, to view in the right perspective the results obtained in experiments on animals by dietary measures in connection with the study of malignant growth, unless the reciprocal relation of heredity, biology, and chemistry to malignancy be borne in mind. Scientific investigation is becoming daily more like the game of chess, in which not only the position and the respective possibilities of action of the king and the queen, but of two bishops, two knights, two castles, and eight pawns may have to be considered if the counter-moves of the opponent are to be met successfully.

The rush of modern life and the overwhelming number of scientific publications make it increasingly difficult for workers in a given field even to read the account of investigations which may seem to have no direct bearing on their special line of research. It is in the hope of furthering the common task of all those who are devoting their energies to the study of malignant grwoth and not in any spirit of criticism, that attention is called here to the factors which may explain contradictory findings and unsatisfactory results of the dietary experiments in malignancy.

Few workers in cancer research have had animals of known hereditary tendencies at their disposal for experimental purposes. The importance of the chemical changes produced in the organism by experimental conditions has received practically no attention. Only in rare instances has an attempt been made to follow up, by blood counts and by urine or blood analyses, the metabolic disturbances caused in animals by dietary measures intended to influence malignant growth. Until very recently, an investigator who gave a detailed account of the diets which he used and of the gross changes in appearance and weight of his animals and their tumors, felt that he was doing full justice to the problems which he was attempting to solve. It did not enter into his calculations, that the miscellaneous descent of his animals or, because of it, the chemical reactions of which they were capable, might affect his results. For these reasons experiments in which no attempt was made to ascertain the metabolic disturbances caused by the diets will only be mentioned very briefly; whereas experiments furnishing data at least on changes in the blood or the urine will be discussed in detail. Such discrimination seems warranted, although the writer is keenly alive to the fact that either type of dietary experiment represents a vast amount of tedious and conscientious labor, the force of circumstances doubtless being responsible for much apparent lack of appreciation of factors such as heredity and metabolic disturbances. Future investigations will have to decide in how far information gathered in the absence of data on heredity and metabolism can be looked on as conclusive evidence.

The production of spontaneous epithelial tumors of the tongue in rats fed on oats exclusively by Stahr (1915) is a typical example of the dietary experiment, "lacking in control", as Slye puts it, and, although it is easy to understand that knowledge of the heredity factor could not be obtained, it is very difficult to see why the effect of the type of diet on metabolism should have been completely ignored. Stahr ascribes his results in part, at least, to the chronic irritation produced by the sharp oat husks, which he found imbedded in the tongues of the tumor-bearing animals, but he admits that such husks were also found in the tongues of wild rats, without tumor formation; he mentions that from five to ten months were needed to produce the epitheliomas; that the largest tumors grew in adult rats, while very old rats were not affected; that the best results were obtained by uninterrupted feeding with oats alone, as soon as the animals had been weaned and that tumors failed to develop on other diets. The variations in the size and in the rate of growth of the tumors are referred to as "differences in disposition and constitution of the rats", but no attempt is made to trace the metabolic disturbances caused by the ill-balanced diet. Stahr used neither blood counts, nor any kind of chemical analysis. Yet such tests might have helped to answer many questions: why did the tumors fail to appear when the diet did not consist of oats exclusively, why did they grow better in some animals than in others, how and why did prolonged feeding of oats affect the animals? (A detailed discussion of other aspects of Stahr's work will be found in my paper on the relation of the diet, the blood cholesterol, and the lymphoid defence.)

The majority of dietary experiments in cancer research have been made, not on spontaneous tumors such as Stahr produced, but on tumor-grafted animals, the number of takes, the rate of growth of the transplants and the occurrence of metastatic growths being used exclusively as criteria of the influence of a given diet. Attention has already been called to Slye's statement concerning the difference between spontaneous and grafted tumors (page 133) and the general effect of starvation on the growth of transplants has also been discussed (page 126).

An excellent review of the results of dietary measures in transplanted cancer, including the work done from 1907 to 1920 has been published by Sigiura and Benedict. In this paper, to which the reader is referred for details, the effects of both undernourishment and "dietary inadequacies", such as the carbohydrate deficiency of the diet, low protein values, absence of indispensible amino-acids and lack of vitamins, are considered at length, accounts being given of the investigations of Haaland, Stahr, Moreschi, Sweet, Corson-White and Saxon, Alstyne and Beebe, Rous, Funk, Levin, Benedict and Rahe, Drummond and of a long series of experiments by the writer (1920).

Careful study of the foregoing publication reveals a disconcerting lack of harmony in the results obtained and in the conclusions reached by these numerous investigations, and the lack of harmony is even more striking when the full data in the original articles are examined. The following instances may suffice to bear out this statement. Rous, whose observations show the fundamental difference between spontaneous and grafted tumors, found that the "most drastic dieting" left spontaneous tumors unaffected, whereas the growth of grafts could be "prevented or retarded" by underfeeding the new host, but that the "influence of underfeeding varied so much from time to time that no definite conclusions can be drawn". Benedict and Rahe obtained a retardation of the growth of tumor grafts with an artificial diet, free from water-soluble vitamins. Drummond, on the other hand, came to the conclusion: "Only the most drastic restrictions, involving serious loss of weight on the part of the host, have any influence on tumor growth". Levin was unable to corroborate the findings of Funk with regard to a reduction in the number of takes in chickens inoculated with a Rous' chicken sarcoma when, prior to inoculation, polished rice alone had been given for some days; nor could he further the development of the sarcomatous tumors, as Funk had done, by feeding unpolished rice or by adding yeast to the polished rice diet. The experiments of Sigiura and Benedict, although numerous and carefully conducted, show contradictory results: in one group of animals (rats) the banana-casein diet produced "a decidedly retarding influence on tumor growth and an inhibitory action on tumor susceptibility"; in another group "The grafted tumors grew with equal rapidity in hosts fed upon banana-casein diet and in the controls".

The fact that in all of these experiments animals were used of unknown descent, with unknown metabolic tendencies complicated their interpretation by bringing "several dark horses into the field", to use a graphic if colloquial expression; it fully explains the divergent or contradictory results. The judicious comment of Benedict and Rahe (1915) that the dissimilarities must be accounted for by "differences in the rats themselves" seems more logical and nearer the truth than the references to the "atypical" characteristics of malignancy including their greater desire for nourishment, which are usually offered in explanation. While the difficulty of obtaining animals of analysed hereditary potentialities is readily granted, the lack of curiosity which kept investigators from endeavoring to find out "what a given diet might be doing within their animals" is rather surprising.

A recent statement of Murray and Woglom in the Seventh Scientific Report of the Imperial Cancer Research Fund (1921, page 47): "Loss of differentiation and atypical cellular characters are so notoriously inadequate as criteria of malignancy in the tumors of man and animals, that they may be left out of account". shows the beginning of a new era in cancer research, an era in which the (by no means new) conception of the body as the "soil" furnishing possibilities of growth to the cells will receive practical consideration. The recent investigations of Bierich (1921) at the Institute for Cancer Research in Hamburg, give evidence of a new trend in the study of malignancy, which promises to lead to more definite conclusions. Bierich's work must be mentioned here, although he did not use dietary measures, but produced experimental tar cancer in mice by application of tar to the skin. He did, however, what no other worker in this field seems to have done before him: he paid attention to the metabolic disturbances which the tar produced in his experimental animals. He observed, "The mice ate a good deal of the tar in their endeavors to remove it". He ascertained through urinalysis that the mice developed albuminuria in from one to eight days after the first application of tar;

that this albuminuria persisted throughout the life of the animals; and he concludes that the local as well as the generalized edema from which the mice suffered could be explained by the kidney lesions found at necropsy and produced by the ingestion of tar. He traced by means of blood counts that during the first weeks of the tar applications leucocytosis and especially lymphocytosis developed simultaneously with hyperkeratosis in the tar-painted areas. Unfortunately the blood counts seem to have been discontinued after the first weeks, for no data are given about the blood pictures which accompanied the formation of papillomas at the end of sixty days, or of the "typically cancer-like growths" which developed in 110 days after continued application of tar.

Bierich's observations on the early renal symptoms in his mice recall the work of Killian and Kast (pages 126 and 128) and suggest that the kidneys, overworked by the elimination of constituents of the ingested tar, may also have failed to eliminate other substances resulting from the metabolic disturbances caused directly or indirectly by the tar, and that the latter may also have played a part in the production of malignancy. This view will be discussed in detail in Chapter XI in connection with the investigation of C. H. Ross on the pitch cancers among Briquette makers.

It is further of interest that Bierich had a chemical analysis made of the tar which he used in his experiments. It was found that the tar contained a very small amount of iron (0.05 per cent), but no arsenic: a fact disproving the contention of Slosse and Bayet (1921) that tar cancers were really "arsenic cancers", because tar always contained traces of arsenic and the stimulation of cell growth by arsenic had been established.

In order to obtain conclusive evidence concerning the effect of arsenic on cell proliferation, Bierich gave liquor potassii arsenitis (Fowler's solution) in doses of 0.001 c.c. daily for a period of forty-one days to twelve mice: none of these mice showed any tendency to tumor formation; nor did one mouse to which Fowler's solution was administered for 120 days develop any kind of tumor. It is to be regretted that no blood counts were made on this group of animals; because mice often develop leukemias and interesting blood changes may have been produced by the prolonged administration of the arsenic compound. The results obtained in this experiment recall the contentions of Forbes Ross (page 116) concerning the effect of potassium on cell proliferation, and suggest that the potassium content of the Fowler's solution may have antagonized the effect of the arsenic. It should be remembered, however, that Bierich shared the fate of other investigators in being unable to control the heredity factor in his mice.

The cholesterol content of the food. The relation of lipoid and especially of cholesterol metabolism to malignant growth will be discussed in Parts II and III, but the experiment of Yutaka Kon of Tokio and one of the experiments of Corson-White must be considered here, because of their bearing on the cholesterol and the vitamin content of the food in experimental diets.

Yutaka Kon (1917) produced adenomas in the stomach of rabbits by feeding lanolin, of which the high cholesterol content has been demonstrated by the extensive chemical analyses of Liffschütz. Twenty-two rabbits were given 5 gm. (about 300 grains) of lanolin for periods ranging from five to 254 days; the staple food of the animals was "okara", a kind of bean stalks. A few of the rabbits died from intestinal disturbances during the first week, but the majority survived. (It is interesting to note that in McCarrison's dietary experiments on wild monkeys gastro-intestinal symptoms also played a prominent part.) The rabbits which were killed at the end of seventy-five days only showed extensive arteriosclerosis, a well-known result of prolonged cholesterol feeding;* those which were killed at the end of 110 days had developed in addition to arteriosclerosis a very marked lipoidosis involving the adrenals, the liver, the diaphragm, the omentum, the connective tissues, and even the sclera and the iris, microscopic evidence of this lipoidosis being obtained. Of nine rabbits fed with lanolin for more than 180 days

* A great many references to work done in the production of arteriosclerosis by cholesterol feeding will be found in Luden's Studies on Cholesterol I-VI.

five developed adenomas of the stomach near the pyloric valve in the lesser curvature; the mucosa was about ten times thicker than normally; the glands had taken on "spiral, sinuous forms"; the cells were abnormally large, but mitotic figures were scanty and there was no invasion except in a few cases, and metastasis was absent. Slye has called attention to the rarity of metastatic growth in animals and mytotic figures are no longer considered essential as a criterion of malignancy, for according to Murray and Woglom many tar cancers "are perfect examples of the high malignancy of skin carcinomata showing practically normal differentiation". Yutaka Kon points out that "The pyloric valve in the lesser curvature of the stomach . . . is the most favored location for the growth of round ulcer and gastric cancer"; and suggests "As cholesterol could not have been reabsorbed by the gastric mucosa, there is no doubt that cholesterinester is reabsorbed from the intestinal mucosa and then transported to the stomach wall by means of the blood and lymph vessels". He, therefore, concludes, "When the interstitial accumulation of lipoids has reached a certain point, the glandular and lining epitheliums take their parts actively in proliferation"; but he does not wish to decide if the adenomas which he produced "can be transformed into carcinoma by still further feeding of lanolin". The work of Kon is noteworthy, because it shows the successive stages of a lipoid infiltration of the tissues coincident with slow, but marked cell proliferation. It is, therefore, greatly to be deplored, that, even in the absence of data on the hereditary tendencies of his rabbits, no effort was made to obtain information about their metabolism during lanolin feeding.

The dietary experiments of Corson-White (1919) on a large series of rats, all grafted with the same strain of a Flexner-Jobling adenocarcinoma, furnish striking evidence, controlled by chemical determinations, of the stimulating effect of cholesterol on cell growth. As these valuable experiments were published in a journal with a very limited circulation, and may thus have escaped the notice of many research workers, the details will be given briefly but as comprehensively as possible.

The object of Corson-White's investigation was fourfold, namely: (1) "to decide whether a tumor could grow in a body rendered incapable of growth"; (2) "to study the effects of diets which supposedly exerted their influence through their action on the ductless glands"; as it had been suggested oats and potassium iodid affected these glands, and that eggs stimulated whereas milk inhibited the activity of the thyroid and that the admixture of Sudan III to a normal diet caused atrophy of the thyme; (3) "to investigate the effects to a normal diet of substances supposed to act as stimulators of growth" (vitamines, cod-liver oil, olive oil); and (4) "to examine the effects of the addition of cholesterol to a satisfactory normal and to a deficient diet".

Two types of diet, an adequate normal diet and the inadequate Mendel-Osborne diet were used, thirteen different varieties being obtained by the addition of certain substances. The normal diet consisted of bread, meat, and green vegetables. The Mendel-Osborne diet is composed of gliadin (18 per cent), lard (27 per cent), starch (24.4 per cent), lactose (23 per cent), "salt-mixture" (2.5 per cent) and agar (5 per cent). Numerous, previous investigations had proved that rats fed on the Mendel-Osborne diet remain in good condition but fail to grow, and that the normal diet furnishes normal growth curves. Details about the additions to these diets may be seen in the diagrams (Figs. 1 and 2), which have been added for the convenience of the reader. The duration of the experiments was six months. The work was controlled by the feeding of "normal and sick rats on the normal diet, and of normal rats on an insufficient amount of a satisfactory diet". The effect of castration was studied in normal and on tumor-bearing animals.

The rats used in the investigation were "obtained from the same source" (presumably, the same dealer); they were of the same age and weight; and "litter units", grafted with portions of the same tumor, were always used to test the effect of a given diet.

The tumors resulting from the grafts were removed and weighed at the end of thirty days in every instance, but in each experiment one-half of the group of rats to which a certain diet was given was inoculated as soon as the diet was started, the other half being grafted two weeks later.

Blood counts were made at weekly or monthly intervals. For the blood cholesterol determinations the Bloor method was used, controlled in some instances by duplicate determinations by Weston's method. The size of the animals made it impossible, however, to establish the individual cholesterol standard of each rat, as "the entire blood" had to be removed to make the test; but "the results are based on single tests on each rat", while the "conclusions are based on comparatively large series of rats from each diet".

The conclusions reached by Corson-White are the following:

1. "Diets which provide the most satisfactory growth of somatic cells* are generally most favorable to tumor growth."

2. "Those diets which stimulate most markedly the growth of large tumors give normal growth curves in normal rats, and show a diminution in the number of lymphocytes in the circulating blood and a cholesterol content of the blood equal to normal or higher than normal.

3. "Those diets on which the rats produced the most metastasis gave the highest cholesterol values.

4. "Cholesterol is apparently a factor which favors tumor growth when conditions favorable for its initiation are present."

The importance of certain aspects of Corson-White's experiments warrants calling attention to some details which are not specially emphasized in his account of this investigation, namely (1) the action and the type of vitamines which he used; (2) the relation of castration to the blood cholesterol; (3) the effect of the oat diet on the blood cholesterol and (4) the effect on the development of metastatic tumors of cod-liver oil, olive oil, and cholesterol.

* Corson-White used the term somatic in its literal sense to designate the body as a whole: it is sometimes used erroneously to designate the reproductive cells.

The vitamin content of the normal diet was increased in these experiments by the addition of "autolysed yeast". According to Dunham yeast contains no less than twenty vitamin-units of the growth-promoting B vitamin. Yet the diagrams (Figs. 1 and 2) show that neither the body weight of the rats, nor the weight of their tumors was increased materially by the addition (as compared with the rats on the normal diet alone, the percentages of takes being the same and no metastatic growth resulting from the addition of yeast to the diet. Two groups of rats were used of necessity to study the effect of the normal and of the normal plus yeast diet. It seems possible, therefore, that a difference in the hereditary and metabolic tendencies of the two groups of animals may account for the results obtained; unless the type of yeast was responsible. The recent investigations of Eddy, Heft, Stevenson, and Johnson (1921) have shown that "a number of factors, the concentration of these factors and the rate of diffusion of factor to cell" affect the growth of the yeast cells, so that "the yeast test in its present state is distinctly unreliable as a quantitative measure of vitamin content". These writers also mention that B vitamin is "known to be extremely sensitive to the destructive effect of alkali". If the growth of the yeast cells themselves is thus influenced by many factors, varying degrees of activity are to be expected in yeast derived from different sources. Even if yeast of known quality was used by Corson-White, the autolysis which he mentions, the varied and complex chemical conditions obtaining in the bodies of experimental animals (and in human beings) and the sensitiveness to alkali of the B vitamin may have influenced the results. All of these factors are calculated to complicate matters considerably. It might be of historical interest to add, that the tomato, which is rich in B vitamin (Osborne and Mendel, 1919) has been accused repeatedly of furthering the development of malignant growth: whether or not the tomato deserves this bad reputation, may be decided by future investigation.

The effect of castration on the cholesterol content of the blood has only been studied within recent years (Löwenthal, 1916, Luden, 1916), although the increase of body-weight following castration has been observed from time immemorial. Attention has been called by Luden to the high blood cholesterol values, which often accompany the normal cessation of reproductive activity as well as castration and to the coincident tendency to malignant growth or the rapid growth of tumors. The absence of metastatic tumors in Corson-White's castrated rats, notwithstanding their high cholesterol values and the marked increase in weight of the animals and of their tumors, is noteworthy. Three explanations seem admissible. First, the rarity of metastatic tumors in animals, mentioned by Slye (page 132); second, the influence of hereditary or metabolic factors in the animals belonging to this group; third, the possibility of a satisfactory disintegration of cholesterol within the body, resulting in the transformation of cholesterol into more or less harmless cholesterol derivatives. High blood cholesterol values are not necessarily accompanied by malignancy, whereas poor cholesterol disintegration apparently tends to further malignant growth. The factors which influence the disintegration of cholesterol are discussed in detail in Part II and in Part III, Chapter IX.

The effect of the oat diet observed by Corson-White is of special interest. The stimulation of tumor growth by exclusive feeding with oats, observed by Stahr (page 136) is corroborated, while the metabolic disturbances caused by the diet, which were ignored by Stahr, are given careful consideration. Corson-White calls attention to the fact that the diet "is practically free from cholesterol", and "contains too little fat-soluble A. or water-soluble B. substances for continued growth". He then gives the following details about the general condition of his animals: "The rats sooner or later show rough, coarse fur, yellowish white in color, have large joints, often hemorrhagic extravasations, conjunctivitis and other signs of malnutrition. These rats only gain in weight on addition to the diet of fat-soluble A substances. The tumors, however, in these animals were large and ulcerated early . . . In rats on oats the actual tumor mass was heavier than the entire gain in weight of the animals during this period (thirty days)". The details given by Corson-White furnish conclusive evidence that severe metabolic disturbances, inhibiting normal growth, may act as a stimulus to malignant proliferation: a fact, which suggests that cancer cachexia may be less the result of malignancy than the terminal stage of a certain type of malnutrition caused by profound metabolic disturbances, and the abnormal metabolites thus produced stimulate abnormal proliferation, though they are ill-suited to promote normal growth.

High cholesterol values but average lymphocyte counts and no metastatic growths were found in the oat-fed rats. Transient but fairly pronounced metabolic disturbances, including gastro-intestinal symptoms, a marked rise in the blood cholesterol, accompanied by reduction of cholesterol disintegration and diminution of the number of lymphocytes in the circulating blood were produced by Luden (1917) in herself through the consumption of very large amounts of Scotch oatmeal in the form of "porridge" for a period of eleven consecutive days: temporary "over-working of the pancreas" through the ingestion of much greater quantities of carbohydrates than were usually eaten, is tentatively suggested as an explanation, the blood cholesterol values in diabetes being much higher than normal as a rule; details about this and other dietary experiments are given in the synopsis of Luden's studies on cholesterol in Chapter VII.

The production of metastatic growths in groups of rats by addition of either cod-liver oil, olive oil, or cholesterol to the normal adequate diet, and by the addition of cholesterol to an inadequate diet, is undoubtedly the most remarkable feature of Corson-White's investigation, because of the comparative rarity of metastatic tumors in animals and because all the rats were grafted with portions of the same strain of the Flexner-Jobling carcinoma. It is, therefore, particularly unfortunate, that the hereditary tendencies of the animals used in this experiment must remain a matter of speculation.

The similarity of the results obtained with cod-liver oil, olive oil, and cholesterol, as regards metastatic growth, may be explained by the investigations of Chauffard, Laroche, and Grigaut (1920), who began their research in 1910 and who proved that the ingestion of fat causes a great increase of the blood cholesterol. Siegfried (1918) showed that many chemical reactions, moreover, are retarded by the presence in cancer cells of an abnormal kind of unsaturated fatty acid, while the recent investigations of Gardner and Fox (1921) in London tend to prove that there must be in the body an organ capable of synthesising cholesterol, because "there is under ordinary conditions of diet regularly an excess of output over intake" in man.

The similarity of malignant conditions in man and in animals is generally admitted and the refusal to concede this similarity would stamp all experiments on animals as perfectly useless. A fundamental harmony between the metabolic processes in man and in animals has been proved to exist by numberless investigations, and there is no reason for assuming that, with the exception of herbivorous animals, cholesterol metabolism in animals differs materially from cholesterol metabolism in man. Moreover, rats and human beings are both omnivorous, hence the difference between them can hardly be considered fundamental as regards cholesterol metabolism or the manifestations of malignancy. In a recent editorial of the Journal of the American Medical Association, attention is called to the importance of further investigation of the problems of cholesterol metabolism: these problems are legion, but, as the editor points out: "The search is a project well worth while".

The sum total of the evidence, furnished by the investigations of Corson-White, Siegfried, Chauffard and his collaborators, Kaminer and Freund, Gardner and Fox, taking it collectively as well as the work of many others, supports the conclusion that disturbances of cholesterol metabolism and their relation

* Editorial in the Journal of the American Medical Association, 1922, April 15, vol. 75, 1128-1129.

to the metabolism of fat are closely associated with the development of malignant growth. The influence of hereditary tendencies and of dietary inadequacies on metabolic disturbances is known and admitted. The dietary experiments which Slye is conducting on mice with more than royal pedigrees will undoubtedly furnish valuable information concerning the influence of the diet on malignant growth. Metabolic disturbances may be the result of innumerable factors, all capable of disrupting the chemical functions of the organism. More accurate knowledge concerning the organ or organs which are chiefly responsible for the proper management of cholesterol metabolism will doubtless prove to be of primary importance in the solution of the cancer problems.

BIBLIOGRAPHY

1. Albu, A. and Neuberg, C.: Physiologie und Pathologie des Mineralstoffwechsels. Berlin, Springer, 1906, 251 pp.

2. Bastedo, W.A.: Materia medica; pharmacology; therapeutics, prescription writing for students and practitioners. Philadelphia, Saunders, 1915, 602 pp.

3. Benedict, S.R. and Rahe, A.H.: Studies in the influence of various factors in nutrition upon the growth of experimental tumors. I. Jour. Cancer Res., 1917, ii, 159-178.

4. Beneke: Quoted by Wolff, iii, p. 415.

5. Bierich, R.: Zur Energetik der Bildung maligner Tumoren. Ztschr. f. Krebsforsch., 1921, xviii, 226-260.

6. Bougard: Quoted by Wolff, iii, p. 418.

7. Braithwaite: Quoted by Wolff, ii, p. 85.

8. Bulkley, L.D.: The relation of diet to cancer. Med. Rec., 1914, lxxxvi, 699-702.

9. Bulkley, L.D.: The medical treatment of cancer. New York Med. Jour., 1919, cix, 45-50.

10. Bulkley, L.D.: Proofs of the constitutional nature of cancer. Proc. Am. Assn. Cancer Res., 1921, vi, 185-186.

11. Chauffard, A., Laroche, G. and Grigaut, A.: La cholestérinémie a l'état normal et pathologique. Ann. d. méd., 1920, viii, 69-91.

12. Corson-White, E.P.: Nutritive and blood changes in rats on cancer inhibiting and cancer stimulating diets. Penn. Med. Jour., 1919, xxii, 348-352.

13. Cramer, W.: On the biochemical mechanism of growth. The effect of sodium and calcium ions on the growth of a transplantable mouse carcinoma. Seventh Scient. Rep. Imp. Cancer Res. Fund, 1921, 1-12.

14. Cushny, A.R.: A textbook of pharmacology and therapeutics. 6 ed. Philadelphia, Lea and Febiger, 1915, 514.

15. Da Costa, J.C.: Handbook of medical treatment. Philadelphia, F. A. Davis Co., 1919, 2 vols.

16. Denis, W. and Minot, A.S.: Effects of feeding with calcium salts on the calcium content of the blood. Jour. Biol. Chem., 1920, xli, 357-361.

17. Drummond, J.C.: A comparative study of tumour and normal tissue growth. Biochem. Jour., 1916-1917, xi, 325-377.

18. Dunham, G.C.: The water soluble B vitamine content of certain vegetables. Mil. Surg., 1921, xlviii, 223-234.

19. Dupré de l'Isle: Quoted by Wolff, iii, p. 412.

20. Eddy, W.H., Heft, Hattie L., Stevenson, Helen C. and Johnson, Ruth: Studies in the vitamine content. II. The yeast test as a measure of vitamine B. Jour. Biol. Chem., 1921, xlvii, 249-275.

21. Editorial: Calcium in the body. Jour. Am. Med. Assn., 1920, lxxiv, 1103.

22. Eijkman, C.: Eine Beri-ahnliche Krankheit der Hühner. Arch. f. path. Anat., 1897, cxlviii, 523-532.

23. Esmarch: Quoted by Wolff, iii, p. 416.

24. Forbes-Ross, F.W.: Cancer: The problem of its genesis and treatment. London, Methuen and Co., 1912.

25. Freund, E. and Kaminer, G.: Ueber karzinolytische organische Säuren. Wien. klin. Wchnschr., 1919, xxxii, 1105-1107.

26. Fürth, v.O.: The problems of physiological and pathological chemistry of metabolism. Transl. by A.H.Smith. Philadelphia, Lippincott, 1916, p. 633.

27. Funk, C.: The preparation from yeast and certain foodstuffs of the substance the deficiency of which in diet occasions polyneuritis in birds. Jour. Physiol., 1912-1913, xlv, 75-81.

28. Funk, C.: Die Vitamine. Wiesbaden, 1914, 201 pp.

29. Funk, C. and Dubin, H.E.: A test for antiberi-beri vitamine and its practical application. Jour. Biol. Chem., 1920, xliv, 487-498.

30. Gardner, J.A. and Fox, F.W.: On the origin and destiny of cholesterol in the animal organism. XII. On the excretion of sterols in man. Proc. Roy. Soc. London, 1921, s.B., xcii, 358-367.

31. Garrison, F.H.: An introduction to the history of medicine. 3 ed. Philadelphia, Saunders, 1921, 942 pp.

32. Goldberger: Quoted by Palmer, W.M.: Metabolism. Nelson's Loose-Leaf Living Med., 1920, iii, 33.

33. Gröbly, W.: Ueber die Bedeutung der Zellkernstoffe (Nukleoproteide) für den Organismus. Eine Studie zur Frage der endokrinen Sekretion einerseits und der Krebskonstitution andererseits. Arch. f. klin. Chir., 1921, cxv, 170-260.

34. Gruner, O.C.: A study of the changes met with in the leucocytes in certain cases of malignant disease. Brit. Jour. Surg., 1915-1918, iii, 506-525.

35. Haaland, M.: Beobachtungen über natürliche Geschwulstresistenz bei Mäusen. Berl. klin. Wchnschr., 1907, xliv, 713-719.

36. Haviland: Quoted by Wolff.

37. Hawk, P.B.: Practical physiological chemistry. Philadelphia, Blakiston's, 1907, 208 pp.

38. Hendley: Quoted by Wolff, ii, p. 89.

39. Hochenegg: Quoted by Wolff, iii, p. 415.

40. Hoffman, F.L.: The mortality of cancer throughout the world. New Jersey, Prudential Press, 1915, 826 pp.

41. Hoffman, F.L.: The mortality from cancer in the western hemisphere. Jour. Cancer Res., 1916, i, 21.48.

42. Hopkins, F.G.: Report on the present state of knowledge concerning food factors (vitamines). London, H. M. Stat. Off., 1919, 107 pp.

43. Horst: Quoted by Host.

44. Host, H.F.: On chloride metabolism. Jour. Lab. and Clin. Med., 1919-1920, v, 713-729.

45. Killian, J.A.: The influence of anesthesia and alkali therapy on the diastatic activity and sugar of human blood. Proc. Soc. Exper. Biol. and Med., 1917, xv, 17-18.

46. Killian, J.A. and Kast, L.: A study of significant chemical changes in the blood coincident with malignant tumors. Arch. Int. Med., 1921, xxviii, 813-826.

47. Kon, Y.: Adenoma-formation in the stomach of rabbits by feeding with lanolin. Jour. Med. Res., 1916-1917, xxxv, 337-347.

48. Levin, I.: The relation between vitamines and tumor growth. Proc. New York Path. Soc., 1916, xvi, 93-100.

49. Loewenthal, K.: Zur Physiologie des Cholesterinstoffwechsels, Beziehungen zwischen Hoden und Cholesterinstoffwechsel. Beitr. z. path. Anat. u. z. allg. Path., 1916, lxi, 564-569.

50. Luden, Georgine: Studies on cholesterol. IV. Experiments concerning the relation of diet, the blood cholesterol, and the "lymphoid defense". Jour. Lab. and Clin. Med., 1917-1918, iii, 141-174.

51. Lusk, G.: Elements of the science of nutrition. 3 ed. Philadelphia, Saunders, 1917, 641 pp.

52. McCarrison, R.: Deficiency disease: with special reference to gastro-intestinal disorders. Brit. Med. Jour., 1920, i, 822-826.

53. McCarrison, R.: Faulty food in relation to gastro-intestinal disorder. Jour. Am. Med. Assn., 1922, lxxviii, 1-8.

54. McCollum, E.V.: The newer knowledge of nutrition. 2 ed. New York, Macmillan Co., 1922, 449 pp.

55. Massaglia, A.C.: The internal secretion of sandstroem's glands. Parathyroid hypofunction and eclampsia. Endocrinology, 1921, v, 309-324.

56. Mayo, W.J.: The relation of cancer to the prolongation of human life. Surg., Gynec. and Obst., 1920, xxx, 23-26.

57. Moraczewski: Quoted by Wolff, iii, p. 418.

58. Moreschi, C.: Beziehungen zwischen Ernährung und Tumorwachstum. Ztschr. f. Immunitätsforsch. u. exper. Therap., 1909, ii, 651-675.

59. Müller, v. and Laudenheimer: Quoted by Host.

60. Murray, J.A. and Woglom, W.H.: Experimental tar cancer in mice. Seventh Scient. Rep. Imp. Cancer Res. Fund., 1921, 45-61.

61. Myers, V.C. and Short, J.J.: The estimation of chlorides in blood. Jour. Biol. Chem., 1920, xliv, 47-53.

62. Osborne, T.B. and Mendel, L.B.: Nutritive factors in plant tissues. II. The distribution of water-soluble vitamins. Jour. Biol. Chem., 1919, xxxix, 29-34.

63. Pettibone, C.J.V.: An intermediate textbook of physiological chemistry. St. Louis, Mosby, 1917, p. 163.

64. Pruche, A.: Biochimie élémentaire du serum. Presse méd., 1921, xxix, 35-96.

65. Robin, A.: Sur la retention des chlorures dans le foie et le sang chez les cancereux. Compt. rend. Acad. d. sc., 1913, clvi, 1409-1410.

66. Robin, A.: Les pigments; les matières albuminoïdes; l'acidité urinaire; les matières ternaires, les matières minérales globales; la chaux, la magnésie, la potasse et la soude chez les cancéreux. Bull. Acad. d. méd., 1914, 3 s., lxxii, 81-84.

67. Robin, A.: [Silica, calcium and magnesium in cancer tissue.] Bull. Acad. d. méd., 1922, lxxxvii, 128-132.

68. Ross: Quoted by Wolff, iii, p. 418.

69. Rous, P.: The influence of diet on transplanted and spontaneous mouse tumors. Jour. Exper. Med., 1914, xx, 433-451.

70. Rous, P.: The influence of dieting upon the course of cancer. Bull. Johns Hopkins Hosp., 1915, xxvi, 146-148.

71. Sawyer, J.: Note on the causation of cancer. Lancet, 1900, i, 848-849.

72. Shipley, P.G., Park, A., McCollum, E.V. and Simmonds, S.: Studies in experimental rickets. Practical Medicine series. Chicago Year Book Pub., 1921, iv, 179-180.

73. Siegfried, M.: Über die Beeinflussung von Reaktionsgeschwindigkeiten durch Lipoide. Biochem. Ztschr., 1918, lxxxvi, 98-109.

74. Sherrett, F.B.: The cancer problem - a suggestion. Brit. Med. Jour., 1907, ii, 1206-1207.

75. Slosse and Bayet: Quoted by Bierich.

76. Slye, Maud: The relation of pregnancy and reproduction to tumor growth. Studies in the incidence and inheritability of spontaneous tumors in mice. Problems in the behavior of tumors. Tenth report. Jour. Cancer Res., 1920, v, 25-52.

77. Slye, Maud: The influence of heredity in determining tumor metastases. Studies in the incidence and inheritability of spontaneous tumors in mice. Jour. Cancer Res., 1921, vi, 139-173; 185.

78. Stahr, H.: Durch andauernde Haferfütterung erzeugtes Epitheliom der Rattenzunge. Beitr. z. path. Anat., 1916, lxi, 169-235.

79. Sternberg: Quoted by Wolff, iii, p. 417.

80. Stricker: Quoted by Wolff, ii, p. 86.

81. Sugiura, K. and Benedict, S.R.: The influence of certain diets upon tumor susceptibility and growth in albino rats. Jour. Cancer Res., 1920, v, 373-401.

82. Sweet, J.E., Corson-White, E.P. and Saxon, G.J.: On the influence of certain diets upon the growth of experimental tumors. Proc. Soc. Exper. Biol. and Med., 1913, x, 175-176.

83. Sykes: Quoted by Wolff, ii, p. 89.

84. Van Alstyne, Eleanor V.N. and Beebe, S.P.: Diet studies in transplantable tumors. Jour. Med. Res., 1913-1914, xxix, 217-232.

85. Van den Corput: Quoted by Wolff, ii, p. 88; iii, p. 417.

86. Verneuil: Quoted by Wolff, ii, p. 88.

87. Vigouroux, R.: Le cancer considéré comme maladie constitutionnelle. Rev. de thérap. méd.-chir., 1906, lxxiii, 585-590.

88. Walker, S., Jr.: The relationship between xeropthalmia and fat-soluble A. Jour. Am. Med. Assn., 1922, lxxviii, 273-274.

89. Whitehorn, J.C.: A system of blood analysis. Simplified method for the determination of chlorides in blood or plasma. Jour. Biol. Chem., 1920-1921, xlv, 449-460.

90. Williams, W.R.: The natural history of cancer, with special reference to its causation and prevention. New York, Wm. Wood and Co., 1908, pp. 216; 310.

91. Wolff, J.: Die Lehre von der Krebskrankheit, von der ältesten Zeiten bis zur Gegenwart. Jena, Gustav Fischer, Bd. i, 1907; Bd. ii, 1911; Bd. iii, 1913.

PART II.

DATA, CONSIDERATIONS, AND PERSONAL OBSERVATIONS LEADING TO THE

BIOCHEMIC CONCEPTION OF CANCER

Chapter VI

THE PERPLEXING DISHARMONY BETWEEN CLINICAL OR EXPERIMENTAL OBSERVATIONS AND THE EXPLANATIONS OF MALIGNANT GROWTH FURNISHED BY THE COHNHEIM THEORY AND THE "CELLULAR" CONCEPTION OF NEOPLASIA

The peculiar, characteristic pallor associated with carcinoma which "once seen, is never forgotten" (Grawitz), was pointed out by Frederick von Mueller with special emphasis to his pupils when I began to study medicine. This cancer pallor first suggested to me the possibility that the chemical composition of the blood might somehow be responsible for the development of carcinoma. No doubt lack of knowledge and the association of ideas, which makes us involuntarily connect a patient's pallor with his blood, were largely accountable for this somewhat vague deduction. Nevertheless, the train of thought uniting cancer and blood-chemistry, once started, could not be eradicated altogether, even by subsequent teaching.

Several years later, during my internship at the Surgical Poli-clinic in Munich, an incident, trifling in itself, revived my interest in the chemical composition of the blood in malignant disease. My chief, Professor Klaussner, often used to remark while operating on goiters, of which so many are found in Bavaria,* "I do not like the look (Beschaffenheit) of that blood; I hope this is not going to be malignant". This remark was made about cases presenting

* The number of malignant goiters that were found at operation has left me with the impression that cancer of the thyroid may be more common in Bavaria than it is elsewhere, although on the whole the thyroid appears to be unsuitable soil for carcinoma. Williams reports only seven cases in a total of 7297 cases of cancer, and Tanchou (necropsy material) eight in 9118, or approximately 1:1000. Wilson found a much higher incidence, 1.41 per cent in his analysis of 9348 thyroids that had been removed at the Mayo Clinic up to 1918. In this series the glands with microscopic evidence of malignancy numbered 132, including 109 epithelial tumors, eighteen sarcomas and five mixed tumors, that is, carcinoma and sarcoma combined.

no symptoms of malignancy, such as marked hardness of the gland or manifest involvement of the surrounding tissues. His staff therefore, junior-like, decided to check up. To our surprise careful microscopic examinations proved him to be right in a series of seven of ten cases. But he could not give any definite reason for his impression concerning the blood, all he could say was that it looked "peculiar, more transparent" (mehr lack-farbig) to him. I do not attach much importance to this incident, but it again focussed my attention on the chemical (or physical) properties of the blood in malignant disease.

It may be surmised that my interest in cancer blood met with little sympathy or encouragement during my service at the Pathologic Institute under Professor von Borst. Gradually, as I became more familiar with the various lines of investigation in cancer research and with the work of Virchow, v. Hansemann, Ribbert, Haaland, Bashford, Apolant - to name but a few - these first impressions were crowded into the background. But they were not entirely forgotten. For neither Cohnheim's theory of embryonic rests nor the other accepted tenets of cellular pathology seemed to furnish satisfactory or conclusive answers to many questions that presented themselves in connection with the experimental and the clinical observations reported in cancer research.

If the cell alone were to be held responsible for the occurrence of malignant proliferation, how were we to account for the fact that a tumor-graft which grew rapidly in one mouse failed to grow when transplanted into another, but flourished as soon as it had been transferred again to the original animal?* Terms such as resistance and immunity imply that some fundamental difference was admitted to exist between the animals in which tumor grafts could thrive and those in which they declined to grow. But there seemed to be nothing to explain why different animals behaved toward transplants as they were known to do, nor do the terms immunity and resistance give any clue concerning the nature of the difference.

* The recent work of F. C. Mann illustrates this: The transplants of a tumor of a dog and of the tumor of a cat failed to grow in any but the original tumor-bearing animal.

On the other hand, the frequent references to the soil in which tumor cells could or could not multiply suggest that chemical factors either promote or retard the growth of the transplants. But if this were true, then the animal itself, that is, the vital processes regulating the chemical conditions within its body, must furnish the elements that furthered or impeded cell division. And if tumor transplants were thus at the mercy of the chemical conditions prevailing in the different animals, how could spontaneous neoplasms escape being influenced in the same way? Moreover, multiple primary tumors and malignant degeneration of divers organs and tissues in the same individual had been reported. Such a wide distribution of embryonic rests in one body seemed improbable. In a case of generalized carcinomatosis, Wolffian ducts* had been found in the kidney, and they alone showed no proliferation.

The stages of transition from normal to malignant cells had been traced with minute care under the microscope, and precancerous conditions were taken into consideration in surgical procedures. It was admitted that slight injuries become the starting point of highly malignant growths only in certain unfortunate, "predisposed" persons. This recalled the effect of a spark falling into gunpowder. But the factors of the predisposition to malignant growth were unrecognized, they had not been clearly demonstrated, whereas the fate of tumor transplants showed that the individual, chemical(?) make-up of the tumor-bearing animal does affect the rate of division of the cells.

In view of these recognized facts it seemed hardly fair to blame the cells exclusively for the development of malignant tumors: the conception of cancer which referred all the problems of neoplastic growth to the structural imperfections of the cell unit, and appeared to attach little importance to the conditions under which that cell unit had to exist, did not explain any of them. But the facts themselves seemed to point to some driving force goading the cells into lawless and destructive proliferation.

* Case studied by the writer, findings corroborated by L. B. Wilson.

It must be admitted that my conception of the actual character of this driving force and of the factors responsible for its production was as yet extremely vague, though both clinical and experimental data concurred in suggesting that the organism itself was the seat of its production, since the effect of the species, for instance, was recognized. Thus human cancers could not be transplanted into animals, and mouse tumors failed to grow in rats. Moreover, the well-known dictum, starve your mouse, and you will starve your tumor, indicated that this driving force, even if produced in the body and by bodily functions, was also closely associated with the food supply.

When I began to do research work at the Mayo Clinic in 1914 the study of "Zehbe's cells" and their relation to malignant areas drew my attention to the strong affinity of neoplastic tissues for basic hematoxylin. Staining reactions are, after all, chemical reactions between the tissues and the dye. If atypical cells showed such a predilection for stains possessing the chemical characteristic of alkalinity (basic hematoxylin), the inference seemed admissible that the chemical conditions under which the cells developed abnormal proliferation had also helped to produce their chemical affinity for a certain type of stain. This also seemed in accordance with the effect of the soil on the growth of tumor transplants and the other data previously mentioned. Combined evidence, therefore, seemed to favor the conception that chemical factors play an important part in the development of malignant growth.

The foregoing considerations led me to express the opinion that three factors were needed for the effective progress of malignancy: (1) Disturbed internal chemistry; (2) an outside irritant; and (3) a local, chemical defencelessness of the tissues which were first to succumb[3].*

Shortly afterward the experiments of Robertson and Burnett, showing the acceleration of the growth of tumor transplants in rats by means of intravenous injections of cholesterol, gave me a clue with regard to one chemical factor

* Proceedings of the American Association for Cancer Research. Eighth Annual Meeting.

at least that might be responsible for the occurrence of abnormally rapid cell proliferation. Robertson and Burnett had used intravenous injections and had injected the cholesterol into the side of the animal opposite the tumor; the blood stream, therefore, had manifestly carried the growth-promoting substance to the tumor cells. This proved, at any rate, that the chemical composition of the blood does affect cell proliferation. It became the basis of investigation for the work which I have reported under the heading Studies on cholesterol I to VI.

BIBLIOGRAPHY

1. Garrison, F.H.: An introduction to the history of medicine. Philadelphia, Saunders, 2nd ed., 1917, 905 pp.

2. Grawitz, E.: Klinische Pathologie des Blutes. Leipzig, 1911.

3. Luden, G.: Studies on a cell (Zehbe's) found in cases of human carcinoma and mixed tumor. Jour. Cancer Res., 1916, i, 115-116.

4. Luden, G.: Studies on cholesterol. I. Observations on cholesterol retention as a factor in cell-proliferation. Jour. Lab. and Clin. Med., 1915-1916, i, 662-676.

II. Observations on the changes in the cholesterol content of the blood of goats, following cholesterol feeding alone, roentgen treatment alone, and cholesterol feeding combined with roentgen treatment and subsequent castration. Jour. Biol. Chem., 1916, xxvii, 273-297.

III. The influence of bile derivatives in Bloor's cholesterol determination (Preliminary report). Jour. Biol. Chem., 1917, xxix, 463-476; also Jour. Lab. and Clin. Med., 1917-1918, iii, 93-109.

IV. Experiments concerning the relation of the diet, the blood cholesterol and the "lymphoid defence". Jour. Lab. and Clin. Med., 1917-1918, iii, 141-174.

V. The blood cholesterol in malignant disease and the effect of radium on the blood cholesterol. Jour. Lab. and Clin. Med., 1918-1919, iv, 849-964.

VI. The value of blood cholesterol determinations and their place in cancer research. Jour. Lab. and Clin. Med., 1918-1919, iv, 719-735.

5. Mann, F.C.: Attempts to obtain a transplantable tumor in the higher species of animals. Jour. Cancer Res., 1919, iv, 331-347.

6. Robertson, T.B. and Burnett, T.C.: The influence of lecithin and cholesterin upon the growth of tumors. Jour. Exper. Med., 1913, xvii, 344-352.

7. Tanchou: Quoted by Williams.

8. Williams, W.R.: The natural history of cancer, with special reference to its causation and prevention. London, Heineman, 1908, 214 pp.

Chapter VII

SYNOPSIS OF STUDIES ON CHOLESTEROL I, II, III, IV, V, and VI.

A brief review of my previous publications is given in this chapter to show how the conception of cancer as a disease of metabolic origin developed and took shape in my mind in the course of my investigations.

Study I. Observations on cholesterol retention as a factor in cell proliferation

In this paper the occurrence of multiple primary tumors and of malignant proliferation in different tissues of the same organ is discussed; personal observations are reported on a tumor of the elbow which contained no less than four types of malignancy: osteoma, sarcoma, chondroma, epithelioma. The original article contains photomicrographs of this tumor. The occurrence of multiple primary tumors suggests the presence of some agent capable of goading divers tissues into proliferation. It also suggests that this agent might be of a chemical nature, since bacteriologic investigations have failed to demonstrate the parasitic etiology of malignant growth. The following points are taken into consideration:

1. The chemical anomalies found in malignant conditions; the increase of the blood sugar, of the urinary nitrogen and the urinary sulphur, and the glycogen content of tumors, which is proportionate to their degree of malignancy.

2. The effect of cholesterol, a chemical substance, on cell proliferation: (a) the increase of the cholesterol content of the mother's blood during pregnancy and its return to normal after delivery, in man and in animals;*

* The increase of the blood cholesterol during pregnancy has recently been denied by Pacini. But in testing the Pacini method, I have found that the results obtained by this method vary greatly in different samples of blood; in some the total cholesterol is extracted at one boiling (of thirty minutes) and the values obtained tally with those of the same sample by the Bloor II method; in others, repeated extractions each furnish some more cholesterol, the sum total equalling the Bloor II values. A great number of parallel tests on different samples were made with both the Bloor and the Pacini methods. Difficulties in obtaining Thorn extractors

(b) the increased rate of division of paramecium after the addition of cholesterol to the culture medium; (c) the increase of the mass of cells constituting the chick embryo and the parallel decrease of cholesterol content in the yolk of the hen's egg during the process of hatching; and (d) the increase of the growth of tumor grafts after intravenous injections of cholesterol.

3. The organs concerned with the regulation of cholesterol metabolism, namely, the adrenals, liver, spleen, gonads, and Aschoff's endothelial apparatus, as shown by numerous experiments made by independent observers.

The evidence furnished by this bibliographic review seemed to warrant several deductions; first, that the body chemistry is abnormal in malignancy, second, that cholesterol in some way promotes cell multiplication, and third, that impairment of the organs which regulate cholesterol metabolism might be expected to disturb the cholesterol balance in the body, whereas an increase of cholesterol might also be expected to promote undue cell proliferation. In order to verify the accuracy of these deductions the following work was undertaken:

1. Double adrenalectomised spermophiles (gophers) were exposed to small but repeated doses of x-rays. The results obtained were an increase of the normoblasts in the blood up to 10 per cent and invasive proliferation of the epithelium of the urinary bladder, involving the muscular stratum. Mere exposure to equal dosage of roentgen rays failed to produce these changes in the controls. This showed that the absence of the adrenal, the chief regulator of cholesterol metabolism, must have played some part in the results obtained in the experimental animals.

2. The blood cholesterol values were determined in a number of

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halted these investigations, which are to be resumed. Some difference in the chemical configuration of the cholesterol in individual samples may account for these findings. In the meantime Pacini's conclusions with regard to the blood cholesterol in pregnancy as determined by his method seem to me to be open to doubt, inasmuch as they contradict the findings of many other observers. For it is obvious that in blood samples requiring repeated extraction the use of a single thirty-minute extraction (as recommended by Pacini) will give lower cholesterol values than the actual cholesterol content of the blood warrants.

patients suffering from malignant disease. They were found to be increased in carcinoma, the highest values occurring in a patient in whose blood 33 per cent of normoblasts and 4.2 per cent of megaloblasts had been found _intra vitam_, while microscopic evidence of simultaneous malignant proliferation of divers tissues was found at necropsy.

Further evidence concerning the relation between cholesterol metabolism and malignant growth was furnished by the analysis of a case of melano-epithelioma of the forearm in a woman forty-seven years of age. In this instance certain factors deserve special consideration, namely; (a) there had been bacterial infection of long duration (unrecognized chronic appendicitis) likely to overwork the adrenals; (b) the patient had shown a marked increase in weight, recalling the storage of cholesterol in the body fat, and suggesting a compensatory measure on the part of the organism; (c) a year after hysterectomy and unilateral oophorectomy had been performed a slight injury (bumping) caused a birth-mark which had not given any trouble for forty-seven years to develop into a highly malignant and rapidly growing tumor, necessitating amputation at the shoulder. The tumor showed proliferation of both epithelium and connective tissue. Since the gonads are among the organs that regulate cholesterol metabolism, and since their physiologic activity involves cell production, the inference seems admissible that the elimination of their normal activity by the operation caused an accumulation of cholesterol, and that the latter promoted the undue cell proliferation which occurred after a slight injury and resulted in the death of the patient in less than a year. The blood of this patient taken at operation also had a high cholesterol content.

The foregoing observations appear to warrant the conclusion that insufficient conversion or defective elimination of cholesterol may be a primary factor in the etiology of malignant disease. They also seem to be in accordance with other observations (reported by others) concerning the coincidence of malignancy with the cessation of reproduction, the relation of diet and malignancy (high or low cholesterol intake in food), and the effect of heredity on the incidence of malignant disease, since the hereditary transmission of inefficient organs would lead to an inadequate cholesterol metabolism.

Study II. Observations on the changes in the cholesterol content of the blood of goats following cholesterol feeding alone, roentgen treatment alone, and cholesterol feeding combined with roentgen treatment and subsequent castration

The working hypothesis on which the experiments with spermophiles had been based, namely, that three factors are needed for the effectual progress of malignancy, a disturbance of cholesterol metabolism, an outside irritant, and a reduction of the normal lymphoid defence, was now tested on goats, because these animals appear to be practically free from malignancy.* The results obtained showed that:

1. The cholesterol content of the blood in goats can be increased by cholesterol feeding.

2. Prolonged bacterial infection (mange) reduced the blood cholesterol, but to a less marked degree in the cholesterol-fed animals than in the controls.

3. Roentgen treatment (very diffuse) appeared to lower the blood cholesterol; intercurrent factors (mange) interfered and prevented conclusive evidence on this point.

4. Ether anesthesia caused an initial rise, followed in most instances by a drop of the blood-cholesterol values, (the initial rise may have been

* In Kitt's "Pathologische Anatomie der Haustiere" the fact is emphasized that only a single instance of tumor formation (a benign adenoma of the stomach) has been found in goats. Kitt's data are based on slaughter-house records. All animals are subjected to rigid inspection before slaughter in Europe and a great deal of goats' meat is consumed in Germany and elsewhere. The use of goats, therefore, seemed to offer a certain guarantee against the occurrence of spontaneous tumors.

due to the injection of $\frac{1}{4}$ gr. of morphin, as morphin tends to increase the blood cholesterol). This effect was also observed in dogs, from anesthesia alone without operative procedure.

5. Castration tends to increase the blood cholesterol values, the effect being most pronounced in the cholesterol-fed castrated animal, but it is apparently counteracted by roentgen treatment before and after castration.

6. The increase of the blood cholesterol during pregnancy was observed, but as the animal in question belonged to the group that received combined roentgen treatment and cholesterol feeding, these intercurrent factors forbade definite conclusions.

Study III. The influence of bile derivatives in Bloor's cholesterol determination

The brownish tint which causes a good deal of trouble in the colorimetric determination of cholesterol values in some blood samples, but is absent in others, and of which the origin was a subject of controversy, suggested a series of investigations in which evidence was obtained that bile derivatives were responsible for the troublesome brown-green color found in some types of blood. The following facts were established:

1. In the method first published by Bloor (Bloor I) certain unknown constituents of the blood which cause the brownish tint are eliminated by the use of sodium ethylate. In the Bloor II method no sodium ethylate is added to the ether alcohol extract of the blood before evaporation, and the brownish tint occurs in the majority of the specimens. The values given by the Bloor II test (without sodium ethylate) are always higher in normal blood than those of the Bloor I test, as shown by parallel determinations on 374 blood samples with both methods. In normal blood the difference between the two ranges from 17 to 34 mg. for each 100 c.c. of whole blood.

2. The fact that the blood of jaundiced patients showed a much greater difference between the Bloor I and the Bloor II values (90 mg. or more), and Lifschütz's work on the disintegration of cholesterol to bile derivatives, suggested that the latter might be responsible for the high Bloor II values in icteric blood as well as for the brownish tint in Bloor II tests.

3. The residue of gallstones, from which every trace of cholesterol had been eliminated with the greatest care, was used to determine if a mixture of bile salts and bile pigments (such as occur in icteric blood and in gallstones) could give the Liebermann-Buchard color reaction in the absence of cholesterol. This reaction was found to be constant in its occurrence.

4. The Liebermann reaction of cholesterol-free gallstone derivatives differs somewhat from that of pure cholesterol. The pink stage of the reaction, which (contrary to the data generally given) does not occur in pure cholesterol solutions, is distinctly visible in chloroform solutions of gallstone derivatives, even of a very weak concentration. It cannot be made visible in pure cholesterol solutions of equal or even 400 times greater strength. (The highest concentration of pure cholesterol used in these experiments was 200 mg. of cholesterol in 6 c.c. of chloroform). The pink stage of the reaction given by bile derivatives persists for a long time, and being superimposed on the green tone given by cholesterol produces the brownish tint seen in blood samples in which both cholesterol and bile derivatives are present.

5. The type of Liebermann reaction given by gallstone derivatives can be obtained from the cholesterol free residue of icteric blood.

6. The color reaction of bile derivatives is destroyed by the use of sodium ethylate under conditions parallel with those found in the Bloor I method. The color reaction of pure cholesterol is not affected by the use of sodium ethylate.

7. The Liebermann reaction of cholesterol-free bile derivatives

is due, not to oxy-cholesterol (as suggested by Mueller) but to cholic acid and allied substances in the presence of bile pigments; this was proved by Lifschütz's differential test, which is given in detail in the original.

8. These experiments suggested that parallel determinations with Bloor's original method (Bloor I), and its modification (Bloor II) might furnish valuable information concerning the chemical constituents of the blood in cases of biliary disturbances with or without icterus, which might be supplemented by the dialyzation method of Hoover and Blankenhorn. Such parallel determinations by the Bloor I and Bloor II methods were made in all my investigations and led to the findings reported in Studies on cholesterol IV, V, and VI.

Study IV. Experiments concerning the relation of the diet, the blood cholesterol, and the "lymphoid defence"*

A series of observations on my own blood cholesterol, made between November, 1915, and June, 1916 (about twenty determinations including weekly tests from March 1 to April 22), had shown that on an ordinary mixed diet and in the absence of intercurrent factors, bacterial infection, a severe cold, a slight attack of appendicitis, my cholesterol values remained on a practically even level, 90 mg. for each 100 c.c. of whole blood. This seemed to justify the assumption that if in the absence of intercurrent factors changes in the blood-cholesterol values could be brought about by dietary measures, the results obtained might be reasonably attributed to the nature of the diet. The current belief that some relation exists between the increased consumption of meat and the incidence of malignancy and Murphy and Morton's observations, suggesting that the lymphocytic reaction is one of the body's natural means of defence against malig-

* In this and in subsequent papers the term lymphoid defence represents the combined percentages of the small and the large lymphocytes only. The transitionals are not included, as hematologists do not agree about the class of white cells to which they should be assigned; Grawitz considers them prototypes of the polymorphonuclears, Simon, large lymphocytes, and Ziegler, myelocytoid cells.

nant proliferation, were the basis of my investigations concerning the effect of the diet on the blood cholesterol. Two factors had previously been determined, namely:

1. The cholesterol content of some fifteen articles of food as given by the Bloor method. It had been found that the Bloor I values of normal human blood ranged from 70 to 100 mg. for each 100 c.c., egg yolk contained 888 mg., chicken breast (roasted) 127 mg., butter 157 mg., cream 61 mg., raw milk 28 mg., and roast beef 63 mg. In other words, the articles of food used by preference to build up patients, for example, eggs, chicken, butter, and cream, had relatively the highest cholesterol values. Roast beef was lower than at first expected. Oatmeal (porridge) contained no cholesterol whatsoever; this latter fact is of importance with regard to a subsequent dietary experiment. Moreover, the Bloor I and Bloor II values were identical in nearly all articles of food; when the Bloor II values were higher, as in butter, some coloring material, shown by the peculiar color of the test, was responsible for the increase. These observations concerning the equal values in foods with Bloor's two methods seemed to support previous findings about the increase of the Bloor II values in icteric blood by the presence of bile derivatives.

2. The cholesterol content of the blood during the period of digestion. Hourly tests made on my own blood after ingestion of various types of meals had shown a distinct rise followed by a return to normal at the end of four hours if meat and eggs had been taken, whereas normal values were obtained within an hour after the consumption of only bread and butter and tea. After the ingestion of meat the rise of the blood-cholesterol values seemed to persist longer than after the consumption of eggs, although eggs have a relatively higher cholesterol content than meat. The effect of the following diets was studied:

A. Gruner's diet for three days. This diet consisted of milk and water, lettuce and toast. Result: A marked drop of the Bloor I values from 114 to

62 mg.; an increase of the Bloor II values, shown by the dark brown-green color of the tests, although the exact amount of the increase could not be determined as the tests were too brown to match in the Hellige colorimeter, and an increase of the lymphoid defence from 26 to 33 per cent.

D. Exclusive meat diet for eight days. Result: A gradual increase of the Bloor I values from 62 to 124 mg., accompanied by a relative decrease of the Bloor II values and followed by an attack of diarrhea on the seventh day, resulting in a noticeable drop of the Bloor I values and an increase of the Bloor II values on the eighth day, which suggested an automatic attempt at safeguarding the organism from accumulating too much blood cholesterol (the alternating constipation and diarrhea found in the history of so many cancer patients seems to confirm this interpretation). Simultaneously the following changes occurred in the blood picture: A steady decrease of the lymphoid defence from 33 to 17 per cent; marked increase of the atypical polymorph neutrophils (ring-like nuclei and bizarre nuclei, showing solid discs or bars, or resembling the letter L or J) from 0.5 to 9 per cent. Preliminary observations had shown that these atypical cells do not exceed 2 per cent in normal blood. Gruner attaches diagnostic significance to their presence. He found them numerically increased in cases of malignancy and could increase their number in his own blood by consuming a great deal of meat, especially pork. The atypical neutrophil leukocytes considered in these counts were chosen because no mechanical effect in the making or staining of the smears seemed capable of producing the peculiar shape of their nuclei. Moreover, in a patient suffering from carcinoma of the sigmoid 10 per cent of these atypical cells, a lymphoid defence of only 11 per cent, and equal values with the Bloor I and II methods of 139 mg. had been found before radium treatment, whereas after radium treatment the atypical neutrophils went down to 3 per cent, the lymphoid defence rose to 33 per cent and the Bloor I values dropped to 80 mg. (Bloor II, 96 mg.).

C. Exclusive vegetable diet for ten days, immediately following exclusive meat diet. Result: A gradual decrease of the Bloor I values from 114 (after diarrhea) to 67 mg. on the sixth day, after which a new level of 80 mg. was reached, which persisted for the remaining days. The Bloor II values were consistently 20 mg. higher than the Bloor I values. The difference between the two methods was greatest on the sixth day: Bloor I, 67 mg., Bloor II, 104 mg., giving a difference of 37 mg. The lymphoid defence rose steadily from 17 to 33 per cent, and the atypical neutrophils practically disappeared (ring forms 0.5 per cent, bizarre forms 3 per cent). In order to gauge the value that might be attached to the percentages found for the lymphoid defence and the atypical cells and to estimate the element of error in these counts blood smears had been made at intervals for three consecutive days, the total differential count, lymphoid defence, and the number of atypical cells being determined by three independent workers. Comparison of the results thus obtained showed that the element of error due to individual counting never exceeded from 2 to 3 per cent in perfect smears. These experiments proved that both the chemical composition of the blood and its cytology could be influenced by the nature of the food that was used.

Two seemingly unrelated problems formed the basis of another dietary experiment; namely, the cause of epithelial proliferation on the tongues of rats fed exclusively on oats by Stahr (who had paid no attention to chemical or cytologic changes in the blood of his rats), and the much disputed ability of body cells to synthesise cholesterol from cholesterol free food.

It will be remembered that oatmeal porridge had been found to contain no cholesterol. In order to establish the effect of cholesterol free oats or oatmeal on the cholesterol content of the blood and its cytology a diet meeting the following requirements was devised: (a) The diet, if possible, must consist of Scotch oatmeal (ground oats) exclusively; (b) it must contain all the elements needed to maintain the metabolic balance, that is, the number of calories and proportional amounts of protein, carbohydrates, and fat, corresponding to the age, sex and occupation of the experimenter (as given by Mürah and Friedwald), and (c) the additional food stuffs that might be needed must contain as little cholesterol as possible.

D. Oatmeal diet for six days, immediately followed by ordinary mixed diet for seven days. Result: A gradual increase of the Bloor I values from 89 to 133 mg. on the fifth day, on which the Bloor II values were 140 mg. (difference only 7 mg.); diarrhea on the fifth and sixth days, lowering the Bloor I values and reestablishing a difference of about 20 mg. between the Bloor I and II values. The changes in the lymphoid defence were not so marked during the oatmeal diet as they had been during the all meat diet, but the ring-form of the atypical neutrophils increased from 3 to 6 per cent. A gradual increase in weight from 134.5 to 136.5 pounds occurred during the first five days of the experiment. This increase slowly disappeared during the use of the ordinary mixed diet. The slight rise of the blood cholesterol, however, which accompanied the return to 134.5 pounds (weight that had been consistently maintained for several years) showed some fat must have been accumulated during the excessive consumption of oatmeal.* The additional two pounds were not, therefore, due solely to a hydremic condition of the tissues, resulting from an increased intake of water; oatmeal absorbs no less than four times its volume of water during the process of cooking. I might add that at first an attempt had been made to use one pound of raw oatmeal each day (1850 calories) as the basis of the diet. But since oatmeal increased its bulk no less than four times on cooking, the consumption of a pound of the cereal, in this magnified form, proved a physical impossibility. A compromise had to be resorted to and the basis of the diet was changed to three-fourths of a pound of oatmeal (for details see original paper). Owing to flatulence and splenic pain the oatmeal diet proved by fat the most uncomfortable of my dietary experiments.

* That cholesterol is stored in fat has been proved by the work of Rothschild on the blood cholesterol in starvation, and of Hueck and Wacker and others.

No satisfactory explanation could be found for the rise of the blood cholesterol on a practically cholesterol-free diet. Perhaps a relative over-working of the pancreas might account for the increase of the blood cholesterol. High cholesterol values are common in diabetes and the pancreas is known to be the chief regulator of carbohydrate metabolism. The work of Mueller has shown that the pancreas also is concerned in the esterification of cholesterol. Although I did not consume a greater amount of carbohydrates in this diet than was theoretically justified, I was nevertheless eating far more carbohydrates during the oatmeal diet than I had been in the habit of consuming. It seems possible, therefore, that my pancreas, having to attend to the metabolising of relatively more carbohydrates than it was used to, somewhat neglected the esterification of the cholesterol, and that the latter piled up in the blood in consequence. Of course this cannot be proved. But the exceedingly small difference* between the Bloor I and II values (only 7 mg.) on the fifth day suggests that some such disturbance of cholesterol metabolism may have occurred.

The result of my dietary experiments may be summarised as follows: (a) The nature of the food is capable of influencing the chemical composition of the blood as well as its cytology; (b) a diet which increases the cholesterol content of the blood apparently tends to weaken the lymphoid defence; and (c) dietetic measures are capable of altering the chemical composition of the blood and its cytology in a relatively short time (six to ten days).

These facts seem to support my statement that "the influence of the diet on cell growth and cell proliferation cannot be discarded as merely hypothetical, especially if we consider that dietary conditions may continue unaltered for months and years, and that the chemical composition of the blood will affect

* Although I was able to show that cholic acid was one of the substances that cause the higher values of the Bloor II method, it is highly probable that cholesterol esters are among the substances that are eliminated from the Bloor I tests by the use of sodium ethylate. This point is under investigation, but no conclusive evidence has been obtained so far. While more conclusive evidence is sought the difference between the two tests may be looked upon as composed of changed cholesterol, or cholesterol split products, possibly including cholesterol derivatives.

the body cells during the entire period". They also emphasise the importance of a question to which is called attention while discussing Stahr's results with his oat fed rats, namely: "Would it not be reasonable to deduce from the foregoing facts that substances supplied in the food and insufficiently metabolised by inadequate organs could become the cause of lawless proliferation, inasmuch as the daily intake of food would furnish a constant stimulant that might bring about a hurried coinage of unfinished atypical cells, embryonic in character, simply because the rate of production did not allow them time to become full grown (that is properly differentiated)?" The observations made in my dietary experiments, moreover, seem to justify the conclusion that dietary measures calculated to reduce the blood cholesterol and to increase the lymphoid defence may yet prove to be of value in the treatment of carcinoma.

Study V. The blood cholesterol in malignant disease and the effect of radium on the blood cholesterol

Isolated observations in the earlier part of 1916 had suggested that radium treatment affected the blood cholesterol values.* But it had seemed advisable to investigate other factors that might influence my findings, namely, the identity of the brownish tint, the effect of dietary measures and the cholesterol values in nonmalignant conditions before I attempted to verify the effect of radiotherapy on the blood cholesterol.

Between November, 1915, and December, 1917, I tested 1069 samples for cholesterol. This number included 1052 blood samples, fourteen determinations on foodstuffs, and three on human pus. Triplicate determinations with the Bloor I method and parallel triplicate determinations with the Bloor II were made on 743 blood samples, giving a total of 4658 determinations. Of these 2196 were made on

* In March, 1916, a patient with an extensive carcinoma (microscopic diagnosis) involving the tongue, the roof of the mouth, and the left upper maxilla, had shown surprisingly low cholesterol (Bloor I) values, that seemed inexplicable at the time. He first stated that he had received no treatment before coming to Rochester, but remembered afterwards that he had received radium treatment about four weeks previously.

pathologic blood. The series included determinations on the blood in seventy miscellaneous conditions, in forty-one cases of pernicious anemia, thirty-seven of exophthalmic goiter, three of myxedema, tested eighteen times at various intervals during the administration of the thyroid hormone (Kendall's thyroxin), nine of sarcoma, ninety-two of carcinoma, before and after radium treatment, and twenty weekly determinations on one patient and seventy-nine determinations on my own blood as normal control and during experimental diets.

These determinations had shown the advantage of parallel tests by the Bloor I and II methods and revealed a number of interesting facts, by furnishing evidence with regard to :

1. The occurrence of two distinct types in human blood. The rapid type of color reaction, which starts somewhat ahead of the standard, and the slow type, in which the color reaction ripens more slowly than the standard. Further observations showed that unless extreme representatives of these two types had to be tested accurate values could be obtained by making readings between ten and twenty minutes after the reagents had been added, simultaneously, to the standard and the sample at a room temperature 20-23° C, but that a fresh standard should be used for each sample. It is obvious that if a sample of slow blood is tested against a fading standard, one that has been in use longer than twenty minutes, the values obtained must be relatively higher than the cholesterol content of the sample would warrant.

The slow type of reaction was generally found in bilious blood (influence of bile derivatives), but the rapid type occurred in various conditions and no data could be obtained with regard to the factors by which the rapid reaction was brought about.

2. The significance of the difference between the Bloor I and II values. It had been shown previously that this difference represents the amount of changed cholesterol (cholesterol-split products and possibly cholesterol derivatives,

esters) present in the blood. Accumulated evidence had proved that there always is a difference between the Bloor I and II values in normal blood, but that in carcinoma this difference is not found in a high percentage of cases,* both the Bloor I and II methods giving "equal", that is, identical values. In a series of 252 determinations in nonmalignant, pathologic cases no equal values could be observed. This suggested some derangement of cholesterol metabolism in malignancy although it was not looked upon as unmistakable diagnostic evidence. As the Bloor I values are given only by pure unchanged cholesterol, the presence of much pure cholesterol (high Bloor I values) seemed well calculated to promote cell proliferation. High Bloor I values were found to occur in 43 per cent of all our cancer patients and in 56 per cent of those who were to have radium treatment, while 54 per cent of those who had high values had also equal values.

The work of Robertson which was published shortly after this paper had been read before the Federation of American Societies of Experimental Biology, and which showed that cholesterol derivatives (esters, changed cholesterol) did not promote the growth of tumor grafts when injected intravenously, whereas pure cholesterol did promote cell proliferation, seemed to support my deduction concerning the occurrence of some derangement of cholesterol metabolism in malignant disease.

<u>3. The establishment of a standard of comparison for blood cholesterol values.</u> The data obtained from about 2000 determinations by Bloor's methods enabled me to establish standards of comparison for the cholesterol values of human blood, the Bloor I values being used as basis of comparison:

(1). Normal values, 70 to 100 mg. for each 100 c.c. of whole blood found in healthy persons on a mixed diet, digestion being excluded, in exophthalmic goiter, and in some cases of sarcoma.

(2). Increased values, 100 to 140 mg. found during the process of digestion and in more or less pathologic conditions (inflammation, acute bac-

* In 53 to 56 per cent of all our determinations on patients suffering from malignancy.

terial infection, and so forth).

(3). High values, 140 to 200 mg. found associated with pathologic conditions only.

(4). Unusual values, more than 200 mg., found in cases of myxodema and in some cases of carcinoma. The normal difference between the Bloor I and II values appeared to range from 17 to 34 mg. for each 100 c.c.

Although differences higher than 34 mg. are found fairly often and probably indicate a temporarily metabolic rate somewhat increased (during a cold, for instance) it seems that differences lower than 17 mg. have a greater clinical significance, inasmuch as they indicate a deficit in metabolic activity, resulting either from temporary exhaustion or from the inefficiency of the organs that regulate the cholesterol metabolism. My reasons for this interpretation will be discussed in Part III.

4. The effect of radium treatment on the blood cholesterol. For purposes of comparison a group of seventy patients suffering from nonmalignant conditions (tonsillitis, gastric disturbances, biliary disturbances, skin diseases, malaria, and so forth) and a group of seventy-two cancer patients, before and after radium treatment, were tabulated diagrammatically. The diagrams show the preponderance of high Bloor I and of equal values in carcinoma before radium treatment; the absence of equal values in nonmalignant cases, and the marked decrease of the high Bloor I values with complete disappearance of equal values in the blood of cancer patients after radium treatment. This proved that the amount of cholesterol-split products in the blood was increased by radium therapy. But it did not explain whether these chemical changes were produced by the photo-activity of radium (since it was known that ordinary, photo-active daylight caused the disintegration of cholesterol) or whether the increase of the cholesterol-split products was caused, indirectly, by the stimulation by radium of the organs regulating cholesterol metabolism. That the latter possibility deserved consideration was suggested

by observations on the blood cholesterol in myxedema and exophthalmic goiter and its relation to the basal metabolic rate (Chapter IX). That the high values found in carcinoma were not due to cell destruction, as is commonly believed, was shown by these same observations.

5. The inversely proportional ratio between the basal metabolic rate and the blood cholesterol values. In thirty-seven cases of hyperthyroidism with metabolic rates ranging from 17 to 90 per cent above normal, low, normal, or only slightly increased blood cholesterol values were found with two exceptions; in one instance the metabolic rate was normal and the Bloor I value high, in the other high equal values were found to accompany a metabolic rate of 8 per cent below normal. The latter patient impressed me as a cancer patient by her coloring and general appearance; thyroidectomy had been performed two years previously. Neither of these two patients could, strictly speaking, be considered to have hyperthyroidism and they had been sent to the metabolism laboratory on a tentative diagnosis based on their general symptoms. In three cases of myxedema unusually high blood cholesterol values had been found when the basal metabolism was from 30 to 39 per cent below normal, while during the administration of thyroid hormone (thyroxin) the increase of the metabolic rate was accompanied by a parallel drop of the blood cholesterol values. This proved that the rate of basal metabolism exerts a direct influence on the cholesterol content of the blood. It also showed that the high cholesterol values found in carcinoma could not be due merely to cell destruction, since:

1. The cytolytic action of radium is generally conceded, yet radium treatment reduced the blood cholesterol (Bloor I) values instead of increasing them.

2. In pregnancy cell production far outweighs cell destruction, but the blood cholesterol of the mother returns to normal shortly after delivery, although the post partum involution of the uterus is accompanied by a considerable

amount of cell destruction and reabsorption.

3. Cell destruction in an egg cannot be said to play a prominent part during the process of hatching, but the high cholesterol content of the egg is used by the chick embryo for the multiplication of its cells.

4. In myxedema, the disease of torpid metabolism par excellence, cell destruction is likely to be very slight, yet the blood cholesterol values in myxedema are unusually high.

5. In exophthalmic goiter, when the basal metabolism is well nigh 100 per cent above normal, the blood-cholesterol values are well within normal.

6. Cell destruction might be expected to accompany increased, rather than sluggish metabolism, yet the physiologic effect of the thyroid hormone is to lower the blood cholesterol values while increasing the metabolic rate.

The metabolic rate, therefore, and not mere cell destruction seems to be responsible for the high blood cholesterol values commonly found in carcinoma. The sum total of these observations seemed to warrant the following conclusions:

1. The Bloor I cholesterol values, indicating the amount of pure, unchanged cholesterol in the blood, might be compared to unconsumed fuel; whereas the Bloor II values represent the amount of pure, plus changed cholesterol; the latter being, like consumed fuel, comparatively harmless, while high Bloor I values indicate an accumulation of unconsumed fuel capable of starting a conflagration.

2. The high percentage of pure, unchanged cholesterol found in the blood in carcinoma represents an opportunity for increased cell proliferation (since pure cholesterol is known to promote cell division) and as such constitutes an element of danger; whereas the changed cholesterol does not contain this element of danger and its increase accompanies the improvement that follows radium therapy.

3. Since carcinoma occurs in the majority of cases when the first vigor of youth is past and metabolism in general tends to become sluggish, the

body of a patient suffering from carcinoma may fitly be compared to a poorly burning stove, incapable of properly consuming its blood cholesterol.

4. The relation of the blood cholesterol to the basal metabolic rate shows that therapeutic measures calculated to increase the rate of metabolism (administration of thyroid hormone, for instance) may prove beneficial to patients suffering from carcinoma.

5. The human body is capable of waging a winning battle against malignancy, since patients with inoperable and hopeless cases of carcinoma are known to have become clinically well, and their recovery may be explained by automatic restoration of the metabolic balance, through spontaneous increase in the activity of the glands which regulate both cholesterol and general metabolism.

Study VI. The value of blood cholesterol determinations and their place in cancer research

Study VI gives a general review of the data collected from November, 1915 to November, 1918 and of the conclusions to which I was led by these observations.

The following points are discussed in detail: (1) The nature of the cholesterol test; (2) the importance of a uniform method for cholesterol determinations; (3) the source of cholesterol intake; (4) the factors that influence the blood cholesterol; and (5) the practical results to be expected in cancer research from the study of cholesterol metabolism.

The nature of the test for cholesterol. Since the test for cholesterol is based on purely chemical reactions and on color comparison (when Bloor's other colorimetric methods are used), it will readily be understood, that technical factors, such as the method of extraction, the use of whole blood or serum only, the color value and tone of the standard, the temperature, and so forth, must control the values in the determinations.

The importance of a uniform method for cholesterol determinations. It is obvious that in clinical work intended to promote our knowledge of the relation between the blood cholesterol values and pathologic conditions a uniform method of procedure should be adopted, since this alone will insure comparable findings. The value of parallel determinations by the Bloor I and II methods was demonstrated by the data obtained with methods, on the apparently inadequate cholesterol metabolism in carcinoma and on the influence of radium treatment on the cholesterol content of the blood.

Valuable information might also be obtained by such parallel determinations concerning the chemical causes of stone formation in cholelithiasis, since the cholesterol content of the bile must be influenced by the cholesterol content of the blood. But the test for cholesterol should never be looked on as diagnostic, for if the information supplied is to be interpreted correctly concomitant factors, as is the case with almost every other clinical test, must always be taken into consideration.

A detailed account is given of the technic used in our determinations, including a description of a new permanent standard and a chart by which the amount of cholesterol in milligrams for each 100 c.c. corresponding to colorimetric readings, can be seen at a glance, because this technic has been based on the determination of more than 1500 individual blood samples, which enabled me to recognize and eliminate various elements of error.

The source of cholesterol intake. Whereas the synthesis by the organism of cholesterol from cholesterol-free material is still a matter of dispute, there can be little doubt that our daily food supply constitutes a constant source of cholesterol intake. Even a strictly vegetarian diet, barring eggs but allowing the use of milk and butter, would result in the consumption of some cholesterol. Butter contains a not inconsiderable amount of cholesterol. The cholesterol content of mushrooms (Agaricus campestris), is even relatively high (140 mg. for each

100 gr.). Egg yolk contains no less than from eight to ten times as much cholesterol as normal blood. It is not surprising, therefore, that eggs and eggnogs are given by preference when the body needs to be built up, as in convalescence or after severe bacterial infections of long duration, which deplete the body's cholesterol. (A table of food values relative to their cholesterol content will be found in this study.)

The advantage of regulating the cholesterol intake in conditions showing a pathologic tendency to hypercholesterinemia requires no further comment. The results obtained in diabetes by dietary measures calculated to reduce the work of the organs regulating carbohydrate metabolisms suggest that similar results might be obtained by a reduction of the cholesterol intake when the lipoid metabolism appears to be weak or impaired.

Factors that influence the blood cholesterol values. Since, as has been shown, there seems to be an inversely proportional relation between the basal metabolic rate and the amount of cholesterol in the blood, it is obvious that factors which influence the general rate of metabolism are likely to influence the cholesterol values. The transient effect of the digestive process on the blood cholesterol has already been discussed. Radium treatment appears to exert a marked influence on the blood cholesterol, decreasing the Bloor I values and increasing the amount of changed cholesterol (that is, the difference between Bloor I and II). No observations concerning the effect of radium treatment on the basal metabolic rate have been published so far; there is little doubt, however, that such observations would greatly further our understanding of the therapeutic value of radium. It has been found that bacterial infection influences the blood cholesterol values: acute infections cause a marked rise in the Bloor I values to be superceded by low Bloor I values in chronic infections such as tuberculosis or syphilis. Ulceration and hemorrhage appear to have the same effect as chronic infections and radium treatment. In a series of determinations on the blood cholesterol in carcinoma of the cervix before and after radium treatment (Chapter IX) both ulceration and hemorrhage seem to have determined our findings to a considerable extent. Whereas a high percentage (56) of high Bloor I values and of equal Bloor I and II values had previously been observed in nonulcerating carcinomas, a surprisingly small number of high values was found in this group of patients.

It will be remembered that the spontaneous regression of tumors, whether grafted or autogenous growths, is usually accompanied by ulceration, sloughing, or hemorrhage; that radium treatment produces these symptoms as well as a general reaction in many cases; that in the results obtained by Coley's treatment the reaction, chills and fever, that is, an increase of the metabolic rate, plays an important part. Consequently the blood cholesterol values seem to be influenced by any process that causes a reaction in the body, that is, by all factors calculated to increase the rate of basal metabolism. This fact should be borne in mind in the interpretation of cholesterol values in clinical diagnosis. It seems to support the view I have previously expressed, that in carcinoma the body might be compared to a poorly burning fire in which metabolic functions are impaired or at least reduced. Unfortunately, no extensive data concerning the metabolic rate, obtained by modern methods, are as yet at hand with regard to carcinoma, but the fact that two patients suffering from cancer who were under my observation had a metabolic rate of 8 and 11 per cent below normal respectively, may be of some significance. Two observations do not constitute much evidence and the slight reduction in the rate of basal metabolism might seem of little consequence. It will be conceded, however, that even a slightly subnormal metabolic rate, existing over a prolonged period, half a lifetime, perhaps, could as effectually disturb the chemical conditions under which the body cells have to exist, and would probably influence the cells far more potently than a marked derangement of metabolism covering a short period only.

<u>Practical results to be expected in cancer research from the</u>

<u>study of cholesterol metabolism.</u> It is admitted that the functional inefficiency of one organ can become the primary cause of perverted metabolism; we need but recall the thyroid in myxedema and the pancreas in diabetes. Chemical disturbances are bound to result from inadequate metabolism no matter whether the organ became inefficient through being "damaged" or whether it was initially inferior through faulty differentiation. Nor can the chemical composition of the blood be expected to be normal under these circumstances. If we admit the hereditary transmission of external features, the hereditary transmission of internal organs seems a foregone conclusion. But if internal organs are transmitted thus, it follows that their inefficiency must become the cause of faulty metabolism, resulting in an abnormal chemical composition of the blood which is bound to effect the life of the cells, their structure, their development, and their rate of proliferation. The hereditary transmission of inadequate organs would thus, as I have suggested in Study I, become a primary factor in the etiology of malignant disease in many cases, while in others the accidental, perhaps even temporary reduction, in the efficiency of these same organs would lead to the same result.

The fact that, according to Rohdenburg's report, no less than 100 cases of malignancy "carefully controlled" showed "complete spontaneous recession", although from a medical point of view their condition might well have been called hopeless, proves that the human body can fight a winning battle against malignancy. Since the patients in question had been pronounced inoperable or had been given palliative treatment only, and none of them had any radiotherapy, the deduction seems warranted that temporarily inefficient organs may somehow manage to recover their working capacity with the result that the metabolic and chemical balance is restored and an apparently incurable condition retrogresses and disappears.

In diabetes, we know of one organ at least that is a causative factor of the disease. Studies of the chemical conditions prevailing in diabetes have furnished the means by which we are now able to achieve therapeutic victories.

Microscopic studies did little to further our knowledge of diabetes, since functional inefficiency of the pancreas is but rarely accompanied by histologic changes. In carcinoma, the organ initially responsible for the disturbances of lipoid metabolism, of which cholesterol metabolism is the chief representative, has not yet been identified. The study of lipoid metabolism is as yet in its infancy. That there is a relation between lipoid metabolism, its anomalies, and lawless cell proliferation seems unquestionable. Blood cholesterol determinations are a means by which our knowledge of lipoid metabolism can be increased; they may help us to recognize the organ or organs responsible for the metabolic anomalies by which proliferation of malignant cells is furthered or brought about; they may assist us in discovering therapeutic measures by which the metabolic anomalies can be rectified. The modern treatment of diabetes is based on chemical investigations; this treatment has proved beneficial to the patient in thousands of cases. Chemical investigations including the study of the blood lipoids may prove equally beneficial to patients suffering from malignant disease. It is for these reasons that determinations of the blood cholesterol, one of the chief blood lipoids, should have a place in cancer research.

BIBLIOGRAPHY

1. Aschoff, L.: Quoted by Soper.

2. Friedenwald, J. and Ruhräh, J.: Diet in health and disease. Philadelphia, Saunders, 1913, 857 pp.

3. Grawitz, E.: Quoted by Luden, Study IV.

4. Gruner, O.C.: A study of the changes met with in the leucocytes in certain cases of malignant disease. Brit. Jour. Surg., 1915-1916, iii, 506-525.

5. Hoover, C.F. and Blankenhorn, M.A.: Dissociated jaundice. Arch. Int. Med., 1916, xviii, 289-303.

6. Hueck, W.: Die Bedeutung der Nebennieren für den Kohlenhydrat - und Cholesterinstoffwechsel und über die Beziehung des Cholesterins zum Fettstoffwechsel. Centralbl. f. allg. Path. u. path Anat., 1914, xxv, 397.

7. Kitt, T.: Lehrbuch der pathologischen Anatomie der Haustiere für Tierärzte und Studirende der Tiermedizin. Stuttg., Enke, 1905, 702 pp.

8. Landau, M. and McNee, J.W.: Zur Physiologie des Cholesterinstoffwechsels. Beitr. z. path. Anat. u. z. allg. Path., 1914, lviii, 667-699.

9. Lifschütz, J.: Die Abbauprodukte des Cholesterins in den tierischen Organen (Gallensäuren). Ztschr. f. physiol. Chem., 1914, xcii, 383-401.

10. Luden, G.: Studies on cholesterol. I. Observations on cholesterol retention as a factor in cell proliferation. Jour. Lab. and Clin. Med., 1915-1916, i, 662-676.

II. Observations on the changes in the cholesterol content of the blood of goats, following cholesterol feeding alone, roentgen treatment alone, and cholesterol feeding combined with roentgen treatment and subsequent castration. Jour. Biol. Chem., 1916, xxvii, 273-297.

III. The influence of bile derivatives in Bloor's cholesterol determination (Preliminary report). Jour. Biol. Chem., 1917, xxix, 463-476; also Jour. Lab. and Clin. Med., 1917-1918, iii, 93-109.

IV. Experiments concerning the relation of the diet, the blood cholesterol and the "lymphoid defence". Jour. Lab. and Clin. Med., 1917-1918, iii, 141-174.

V. The blood cholesterol in malignant disease and the effect of radium on the blood cholesterol. Jour. Lab. and Clin. Med., 1918-1919, iv, 849-864.

VI. The value of blood cholesterol determinations and their place in cancer research. Jour. Lab. and Clin. Med., 1918-1919, iv, 719-735.

11. Mueller, J.H.: The mechanism of cholesterol absorption. Jour. Biol. Chem., 1916, xxvii, 463-480.

12. Murphy, J.B. and Morton, J.J.: The lymphocyte in natural and induced resistance to transplanted cancer. II. Studies in lymphoid activity. Jour. Exper. Med., 1915, xxii, 204-211.

13. Pacini, A.J.P.: Blood cholesterol. Med. Rec., 1918, xciv, 441-446.

14. Robertson, T.B. and Burnett, T.C.: The influence of lecithin and cholesterin upon the growth of tumors. Jour. Exper. Med., 1913, xvii, 344-352.

15. Rohdenburg, G.L.: Fluctuations in the growth energy of malignant tumors in man, with especial reference to spontaneous recession. Jour. Cancer Res., 1918, iii, 193-225.

16. Rothschild, M.A.: Zur Physiologie des Cholesterinstoffwechsels. V. Der Cholesteringehalt des Blutes und einiger Organe im Hungerzustand. Beitr. z. path. Anat. u. z. allg. Path., 1915, lx, 227-231.

17. Simon, C.E.: Quoted by Luden, Study IV.

18. Soper, W.B.: Zur Physiologie des Cholesterinstoffwechsels. Beitr. z. path. Anat. u. z. allg. Path., 1915, lx, 232-244.

19. Stahr, H.: Durch andauernde Haferfütterung erzeugtes Epitheliom der Rattenzunge. Beitr. z. path. Anat. u. z. allg. Path., 1915, lxi, 169-235.

20. Wacker, L.: Das Cholesterin und seine Begleitsubstanzen im menschlichen Depotfett beim Carcinom. Ztschr. f. physiol. Chem., 1912, lxxx, 383-408.

21. Ziegler, E.: Quoted by Luden, Study IV.

PART III

OBSERVATIONS CONCERNING VARIOUS FACTORS CONNECTED WITH THE CANCER PROBLEM AND THE RELATION OF THESE FACTORS TO THE BLOOD CHOLESTEROL VALUES

Chapter VIII

Outline of the considerations suggesting the necessity of researches in seemingly unrelated fields

The investigations which I made between January, 1918, and January, 1920, were intended (1) to check and amplify observations and deductions previously reported, (2) to collect data supplementing the observations of others concerning factors that are considered to have a bearing on the cancer problem, and (3) to correlate these data with the disturbances of cholesterol, that is, of lipoid metabolism that appears to be connected with the etiology of malignant epithelial neoplasia. I hoped that investigations along these lines might also furnish a clue concerning the organs that are initially responsible for the disturbances of cholesterol metabolism which I had observed, although it was to be expected that the plan outlined would necessitate researches in seemingly unrelated fields.

The considerations which led me to adopt this plan of campaign were the following: If malignant epithelial proliferation is caused primarily, as I believed, by a disturbance of the chemical balance, and the latter is due to the inefficiency or to the impairment of the organs that regulate the chemical balance, the cancer problem becomes a chemical problem, and cancer itself a disease of metabolic origin. But in that case the influence of many agents, each capable of lowering the efficiency of those organs, would have to be taken into account. There seems little doubt that the very multiplicity of these agents may have added not a little to the complexity of the cancer problem.

We have been in the habit of ascribing a certain direct influence on the development of cancer to such factors as age, diet, industrial occupation, bacterial infections, and local topographic conditions. If we attribute a direct influence to these factors (though we do not consider any of them as the real cause of cancer), we are at once confronted by the very puzzling observation that they seem to have little or no effect in some cases or groups of cases, while in others their influence can be traced clearly. If, however, we look upon them as factors whose influence is proportional only to the relative efficiency of the organs of which they are likely to impair the chemical functions, the question assumes a totally different aspect, and apparently contradictory findings can be harmonised readily. The effect of age and of bacterial infections on the development of carcinoma furnishes an illustration, although the same applies to other factors such as diet, industrial occupation, and local topographic conditions.

If we attribute the increased incidence of carcinoma after the age of forty-five chiefly to the factor of age as such (Thiersch, for instance, attributes the development of epithelioma to the senile atrophy of the connective tissue, resulting in a preponderance of the bioplastic energy of the epithelium), the occurrence of carcinoma in children seems difficult to explain. But if we consider that the same organs which are likely to become functionally impaired by the wear and tear of life after four or five decades, may also be initially inefficient through faulty development, accidental damage, or hereditary transmission, the occurrence of carcinoma even in young children does not seem inexplicable. For, in children as well as in adults, the body cells are influenced "for weal or woe" by the chemical conditions under which they are obliged to exist. Similarly, the relation of bacterial infections to malignant growth has been the subject of much controversy. (I am not referring to the bacterial etiology of cancer, but to the question whether germ diseases, such as tuberculosis and syphilis, pave the way for malignant neoplasia, coincide with it, exclude it, or are apt to follow in its wake.) Here again we find the most contradictory reports and deductions.

Rokitansky taught at first that tuberculosis and cancer exclude each other, but had to modify his opinion when necropsy material showed unquestionable evidence of the coincidence of carcinoma and tuberculous lesions. Durdel found that parents suffering from carcinoma usually had tuberculous children. His conclusions were based on careful observations during twenty-seven years in Vierzon (France), where he resided during the entire period, and he was able to follow up this tendency even to the third generation in no less than thirty-two cancer families. But Lubarsch observed that tuberculous infections (as well as other acute bacterial infections) were less frequent in patients suffering from carcinoma than in noncancerous persons of the same age; Williams found that with the acute onset of tuberculosis malignant growths disappeared, but that the healing of the tuberculous process was followed by a recurrence of the cancer.

Broders has proved, histologically, the joint presence of malignancy and tuberculous lesions in twenty patients of the Mayo Clinic. Of these twenty patients, four have died, ten were living at the date of writing (1919) and the condition of six is unknown; two of those who survived have had a recurrence, three are in good health, and five have been operated on too recently to be considered. After a detailed analysis of these cases and a very able and comprehensive review of data in the literature, Broders comes to the conclusion that (1) the assumed antagonism between tuberculosis and malignant neoplasia has not been borne out by facts, (2) the ubiquity of tuberculous lesions in adults (according to Naegeli 93 per cent of 420 necropsies on adults more than eighteen years of age)* makes it reasonable to believe that similar findings would prevail in an equal number of persons who die of malignant neoplasia, (3) at necropsy pathologists are apt to be satisfied with their findings of neoplastic conditions and therefore fail to look for tuberculous lesions, whereas in surgical pathologic examinations they are handicapped by a limited amount of tissue, and (4) the prevalence of tuberculosis

* According to the statistics of the Pathologic Institute of Munich 97 per cent of those who died of every known disease or accident, and who had not been known to have a clinical history of tuberculosis, showed tuberculous lesions of some organ at necropsy.

in persons under fifty-five and the prevalence of epithelial neoplasia, especially in persons over forty-five, do not prohibit the association of latent and healed tuberculosis with malignant neoplasia.

The fact that Broders specifies "latent" and "healed" tuberculosis and that none of his cases showed any clinical evidence of an active, florid tuberculosis, is significant for two reasons: (1) namely because of the curative influence of acute bacterial infection on malignant growth, observed by Lubarsch, Williams and others, and (2) because of observations concerning the chemical conditions that prevail in the blood during bacterial infections, and furnish evidence concerning the efficiency or exhaustion of the organs that regulate chemical balance. This is an important point; it will be discussed in Chapter IX.

The relation of carcinoma and syphilis has been the subject of a similar divergence of opinions. Whereas certain observers (Thiry, Alquie, Williams, and others) believed in an antagonism between the two diseases, and some even advocated artificial infection with syphilitic virus as a therapeutic measure against cancer (Didot, Auzias), others were so convinced of the intimate relation between cancer and syphilis, that they instituted antisyphilitic treatment as a regular procedure after operations for malignancy (Langenbeck, Verneuil, Vollmann, Roemer, in 1903, and others). Poirier (1907) proved the existence of a primary syphilitic infection in twenty-seven of thirty-two cases of cancer of the tongue, but Esmarch, Cozzolino and Horand came to the conclusion that syphilitic lesions, like traumatic lesions, pave the way for carcinoma merely by the formation of scar tissue.

The foregoing contradictory views and findings may be harmonized readily if we bear in mind that the chemical conditions in the body, and especially the chemical constituents of the blood, must affect the bacterial invaders as well as the legitimate residents, the body cells; chemical conditions in the body are subject to fluctuations in opposite directions, according to the activity of the organs that regulate them, and the increased activity of any organ is followed by a reduction of activity, if not by exhaustion.

Is there any evidence that at least one chemical constituent of the blood furthers the proliferation of the body cell, but interferes with the growth of pathogenic bacteria? If so we have a right to expect that high percentages of this chemical entity will be found in the blood at the onset of bacterial infection as a defensive measure of the organism, but that prolonged bacterial infection will reduce the percentage; that persisting high values will act as a stimulant on cell proliferation, whereas their reduction by intercurrent bacterial infections will result in a diminution of the neoplastic tendency. In other words, high values of such a blood constituent should confer a certain amount of immunity against bacterial infection, while containing an element of danger with regard to undue cell proliferation.

I hope to show that both my observations on the cholesterol content of the blood, and the independent investigations of Manfredi concerning the effect of cholesterol on the growth of pathogenic bacteria, strongly suggest that while cholesterol appears to promote cell proliferation it is also an active agent in the fight against bacterial invasion. Evidence supporting this statement will be given in detail in Chapters IX and X.

But it should not be forgotten that the problems of blood chemistry are still legion. The exact part played by the various organs that control the blood cholesterol values by no means has been definitely established, although there seems little doubt that both the thyroid and the adrenals are important factors. The effect of cholesterol on bacterial growth threatens, moreover, to link the study of the blood cholesterol with the problems of immunity; a fact which although it suggests great possibilities, also represents much unknown territory, since the chemical features of immunity have received but little attention. The study of endocrinology has already revealed that there is an interaction, based partly on mutual assistance and partly on antagonism, between the organs of inner secretion.

Under these circumstances it is hardly to be expected that the data, which I was able to gather, could be conclusive. Nevertheless they appear to furnish a harmonising element with regard to the contradictory findings that have been reported concerning the relation between bacterial infection and malignant epithelial neoplasia. For if we admit that organs, like all workers, are likely to suffer a reduction of their efficiency by prolonged effort, it is clear that prolonged bacterial infection and the strain of increased activity entailed on the glands that regulate cholesterol metabolism, will result in their functional inefficiency of producing the disturbances of cholesterol balance that appears to be closely associated with epithelial proliferation. Chronic bacterial infection, like tuberculosis and syphilis, would thus pave the way for malignant growth. Stokes' graphic dictum: "In leucoplakia, always look back to syphilis, and ahead to carcinoma", seems to support this explanation.

On the other hand, the high blood cholesterol values commonly found in cancer would help to account for the relative immunity from acute bacterial infections observed by Lubarsch in patients suffering from carcinoma. The recession of tumors during acute infections, reported by Williams and others, seems explicable by the consumption of cholesterol in the process of immunisation, and the resultant lowering of the blood cholesterol values. Reduction of blood cholesterol appears to be an important factor in the beneficial results of radium treatment, since it restricts the opportunity for cell proliferation, as I have pointed out and shall be able to corroborate by further evidence.

It is obvious that toxic influences, resulting from industrial occupation, topographic conditions, or diet, are able to tax and damage the organs regulating the blood chemistry as effectually as do bacterial toxins. Here again the relative strength or weakness of these organs will decide the extent to which their efficiency is likely to be impaired, and the disturbance of the chemical balance will be directly proportional to their functional efficiency.

The relation between various blood constituents, that is, the relative increase of some and the accompanying decrease of others, under the influence of given factors might be expected to furnish some more definite information concerning the organs that regulate the chemical balance in general, and cholesterol metabolism in particular.

I decided, therefore, to make parallel determinations on the following constituents: blood cholesterol, blood sugar, catalase, percentage of hemoglobin, total erythrocytes, total leukocytes, and "lymphoid defence" (the combined percentages of large and small lymphocytes in differential counts*). In each determination one sample of blood taken before breakfast was used for all the tests; blood counts and hemoglobin determinations were made at the same time. A series of observations of this type were made on a large number of persons whose blood was taken weekly or as often as circumstances allowed. The series included patients and volunteers who appeared to be in good health, as well as observations on my own blood for five years (November, 1915 to March, 1920), and for three years on the blood of a patient who had had an amputation of the breast in July, 1917, but was free from recurrence and apparently in excellent health in January, 1920, although the rapidly growing type of tumor found at operation had led Dr. C. H. Mayo to expect a recurrence within a year. The data thus collected have been recorded in the form of curves (Figs. 1, 2, 3, 4 and 5) which with the factors that may have influenced the values in a given case will be discussed in Chapters XI and XII.

Between January, 1918 and January, 1920 I studied 1034 samples of blood. This number includes 660 determinations on human blood, 308 on the blood of goats, fifteen on the blood of rabbits, and six on the blood of dogs, beside five determinations on the cholesterol content of food and ten on that of bile. The determinations on human blood were made in 229 cases of carcinoma, fifty-eight of

* The "transitionals" have not been included in the "lymphoid defence", because their place among the leukocytes is still a matter of dispute among hematologists, some claiming that they belong to the lymphoid series, while others look upon them as precursors of the polymorphonuclear neutrophils.

syphilis, seven of pernicious anemia, two of hyperthyroidism, and fifty-two miscellaneous cases. Forty-two single tests were made on the blood of healthy volunteers as normal controls, and in order to study the effect of the thyroid hormone (Kendall's thyroxin) sixteen determinations were made on the blood of a patient suffering from myxedema. In addition serial observations were made on the blood of nine persons, including 113 on my own blood, fifty-seven on the blood of a cancer patient, twenty-nine on the blood of a patient with lymphosarcoma who was receiving combined radium and roentgen ray treatment, and from ten to twenty-four determinations on the blood of the remaining six persons.

In every instance parallel determinations in triplicate were made with the Bloor I method (with sodium) and with the Bloor II method (without sodium). Observations on the blood sugar and the blood catalase were begun in June, 1919. One hundred two determinations were made on blood sugar and 116 on the blood catalase. Blood counts totalling 1118 had been made as a routine procedure with each cholesterol test since 1916. Apart from these, a great number of observations of a chemical nature had been made in connection with the technic of the cholesterol tests. They will not be discussed here, as they do not come within the scope of this paper, but they will be published elsewhere. They include (1) comparative determinations with the Bloor and Pacini methods; (2) determinations on the ether-alcohol extracts of blood used in the Bloor tests, that had been kept stored for different periods (the object of these investigations was to determine if a disintegration of the cholesterol molecule could be detected in these extracts after they had been kept for some time); and (3) comparative determinations on blood laked with a sodium citrate and with potassium citrate.

It was found that sodium citrate slightly reduces the cholesterol values, the blood sugar, and the blood catalase. Potassium citrate also lowered the cholesterol values but did not affect the sugar and catalase values. Consequently potassium citrate was used for the blood sugar and catalase determinations, but no laking agent was used for the cholesterol tests. The blood is laked by putting it immediately into the ether-alcohol; no clotting occurs. The relative effect of sodium and potassium citrate on the cholesterol values is shown in Figures 2 and 3.

The result of the observations made from January, 1918* to January, 1920, will be discussed under topics as follows:

1. Factors that influence the blood cholesterol values: radium, ulceration, and hemorrhage.

2. Cholesterol and bacterial growth, with reference to the work of Manfredi.

3. The relation of combustion products to the cancer incidence in Rochester, Minnesota.

4. The relation of various blood constituents, and the factors that influence them.

* Investigations prior to 1918 have been published in Studies on Cholesterol I to VI.

BIBLIOGRAPHY

1. Alquie: Quoted by Wolff, iiib, 485.

2. Aumias: Quoted by Wolff, iiib, 485.

3. Broders, A.C.: Tuberculosis associated with malignant neoplasia. Jour. Am. Med. Assn., 1919, lxxii, 390-394.

4. Burdel: Quoted by Wolff, ii, 109.

5. Cossolino: Quoted by Wolff, iiib, 485.

6. Didot: Quoted by Wolff, iiib, 485.

7. Horand, R.: Syphilis et cancer. Cancer sur syphilis au cancer juxtasyphilitique. Toulouse, Dirion et Bailliere, 1908, 192 pp.

8. Esmarch: Quoted by Wolff, ii, 103.

9. v.Langenbeck, B.: Ueber Gummigeschwülste (Granulome, Syphilome). Arch. f. klin. Chir., 1881, xxvi, 265-286.

10. Lubarsch, O.: Ueber den primären Krebs des Ileum nebst Bemerkungen über das gleichzeitige Vorkommen von Krebs und Tuberculose. Virchows Arch. f. path. Anat., 1888, cxi, 280-317.

11. Naegeli, O: Ueber Häufigkeit, Localisation und Ausheilung der Tuberkulose. Virchows Arch. f. path. Anat., 1900, clx, 426-472.

12. Poirier, P.: Quoted by Wolff, ii, 103.

13. Roemer, A.: Ueber Carcinoma auf luetischem Boden. Bonn, 1903.

14. Rokitansky, C.: A manual of pathological anatomy. London, Sydenham, 1855, i, 313-314.

15. Stokes, J.H.: Personal communication.

16. Thiersch, C.: Der Epithelialkrebs, namentlich der Haut. Leipzig, Engelmann, 1865, 78.

17. Thiry: Quoted by Wolff, iiib, 485.

18. Verneuil: Quoted by Wolff, ii, 104.

19. Volkmann, R.: Quoted by Wolff, ii, 104.

20. Williams, W.R.: The natural history of cancer with special reference to its causation and prevention. New York, Wm. Wood and Co., 1908, 519 pp.

21. Wolff, J.: Die Lehre von der Krebskrankheit, von den ältesten Zeiten bis zur Gegenwart. Jena, Gustav Fischer, Bd. i, 1907; Bd. ii, 1911; Bd. iii, 1913.

Chapter IX

FACTORS THAT INFLUENCE THE BLOOD CHOLESTEROL: RADIUM TREATMENT; THE BASAL METABOLIC RATE; BACTERIAL INFECTION; ULCERATION AND HEMORRHAGE

In studies V and VI I called attention to the fact that radium therapy reduces the Bloor I cholesterol values, but increases the amount of cholesterol-split products in the blood. The acceleration of cholesterol metabolism, which these findings indicate, and the manner in which these changes in the chemical composition of the blood may be brought about have been discussed in detail and will not be considered here. Corroborative evidence concerning the effect of radium treatment on the blood cholesterol was obtained in a case of lupus erythematosus degenerating into carcinoma. It was possible in this instance to make a number of serial observations, which greatly enhance the value of the findings (Fig. 6).

The skin lesions on the nose of the patient, a woman aged thirty-five, a native of Holland, presented clinically the typical picture of lupus erythematosus (Figs. 7 and 8). Blue-light treatment failed, however, to have the usual curative effect. Owing to the fact that the patient was a countrywoman of mine, she came to tell me of her disappointment at the negative results of the blue-light treatment. We talked about my work and I asked for a sample of her blood, as I had not had an opportunity to study the blood cholesterol values in the disease from which she was suffering.

To my surprise our determinations revealed a total lack of cholesterol split products, such as I had previously found in many cases of carcinoma; that is, the tests by the Bloor I and II methods gave the same, or "equal", values. I reported these findings to the clinician in charge of the case, Dr. J. H. Stokes, and asked him if in this instance the skin lesions might be disguising a malignant condition. He informed me that lupus erythematosus had been known to degenerate into carcinoma and that Pusey looks upon it as "a disease of the blood". Both these statements seemed to support my conception of malignant growth and to emphasise the importance of the chemical composition of the blood in malignant epithelial neoplasia, which has been the object of all my investigations.

It was decided to obtain conclusive evidence by means of a biopsy. Microscopic examination in serial sections showed the "text-book picture" of lupus erythomatosus, and its unquestionable transition into carcinoma (Figs. 9, 10, 11, 12 and 13).

The patient was advised to take a course of radium treatments. She lived at a considerable distance, in a town where radiotherapy could not be given, and had to come to Rochester for each successive application, so that I was unable to follow the effects of exposure to radium as closely as I wished: Cholesterol determinations could be made only before and after each treatment. Nevertheless the results shown in Figure 6 are striking. There is a consistent drop of the Bloor I values after each exposure and a corresponding increase of the amount of cholesterol-split products in the blood.

Two hundred milligram hours radium were given for each of the first three treatments and 225 mg. hours May 21, 1918, making a total of 825 mg. hours. It is interesting to observe that during the interval which elapsed between the first and the second exposure (November 14, 1917 to January 9, 1918) the Bloor I values rose and that the "equal" values returned (Fig. 6). If, as I have suggested, the Bloor I values represent unconsumed fuel and the cholesterol-split products consumed fuel (or ashes in a general sense) this observation would indicate that the fire, which had been fanned by radium, had died down again after the first treatment, whereas it burned with renewed intensity after the second radium treatment with the result that the "equal" values disappeared for the second time, as Figure 6 shows. The amount of split cholesterol is somewhat less January 11, 1918, than it had been November 14, 1917, but only two days had elapsed since the second exposure to radium and it is possible that an increased rate of cholesterol metabolism had not had time to become fully established. This deduction is supported by our findings March 29, before the third exposure. At that time the blood was found to contain a small amount of split cholesterol, although three months had elapsed during which no radium had been given. The observation is of great importance with regard to the effects of radium treatment. It shows that the patient was apparently beginning to split cholesterol unaided, or, if we retain the simile previously used, that the fire, instead of dying down when fanning ceased, had begun to burn on its own merits. In other words, it indicates a response to treatment. True, the amount of split cholesterol found March 29 is very small, 12 mg. (the lowest normal value is 17 mg.), but it represents a step in the right direction nevertheless. The improvement in the rate of cholesterol metabolism is still more evident before the fourth radium treatment, May 21, 1918. Two months had elapsed since the last application, the amount of cholesterol-split products slightly exceeded the high normal limit, 34 mg., and the skin lesions were scarcely perceptible.

The blood sample used for the last determination which I was able to make on the blood of this patient (May 21, 1918, 3 p.m.) had to be taken three hours after radium treatment of 225 mg. hours, and two hours after a light meal, as the patient was to leave on the afternoon train. I have shown in Study IV that the blood cholesterol values are increased by the process of digestion for three or four hours after the intake of a substantial meal, of eggs or meat for instance, but that a very light meal, such as bread and tea does not affect the values, if the blood is taken at the end of one hour. Consequently, in this instance, the digestive process cannot have influenced the blood cholesterol and the reduction of the Bloor I values must be ascribed to the effect of the radium treatment. The amount of split cholesterol is somewhat less than it was on the same day before radium treatment, presumably because some of the split products had been either eliminated by the intestine or further dissociated into compounds that no longer yielded the characteristic color reaction. The latter assumption is warranted by the fact that the final oxidation products of cholesterol are pale yellow instead of green. Cholesterol tests always fade to a dirty yellow from one to several hours after the reagents, concentrated sulfuric acid and acetic anhydrid, have been added; the time varies according to the concentration (Study III).

As far as is known, the condition of the patient continued to be satisfactory. She came once more for radium treatment, unfortunately during my absence from Rochester; an exposure of 900 mg. hours was given as a prophylactic measure. She has not been heard from since.

The basal metabolic rate. In connection with the foregoing observations on the effect of radium, further evidence concerning the relation between the basal metabolic rate and the blood cholesterol values may be of interest. I suggested in Study V that the beneficial effect of radiotherapy may be due, in part at least, to the activation of the rate of basal metabolism by radium. The basal metabolic rate and the Bloor I cholesterol values were found to be inversely proportional in two cases of myxedema; under the influence of the thyroid hormone the cholesterol content of the blood diminished as the rate of basal metabolism increased. These findings were corroborated by the study of the blood cholesterol values in a third case of myxedema (Case 271237, Fig. 14). Certain details in the history of this case are worth considering.

Figure 14 shows a gradual increase of the metabolic rate from 39 per cent below normal to 5 per cent above normal between May 20 and June 5, 1919. During this period the Bloor I values dropped from 130 to 95 mg. An intravenous injection of 7 mg. thyroxin had been given May 22; two days later the rate of basal metabolism had increased 28 per cent, and the amount of cholesterol split products in the blood was found to be 88 mg. (high normal limit 34 mg.), an observation tending to support the deduction that the amount of split cholesterol is influenced directly by the rate of basal metabolism. This in itself might seem a foregone conclusion, but it assumes a special significance when we consider the lack of cholesterol split products in the blood of many patients suffering from carcinoma and the effect of radium treatment on the blood cholesterol values. The observation seems to support my deduction that carcinoma may be the result of an inadequate rate of general metabolism persisting over a prolonged period and that the body in which cancer develops is comparable to a "poorly burning stove" with an ineffective draught system.

The sudden rise of the Bloor I values (June 10) shown in Figure 14 is hard to explain; the basal metabolic rate was practically normal at the time, -2. Plummer found that the physiologic activity of thyroxin is often delayed in man, reaching its height on the tenth day after administration, and that a single dose functions in the body for about three weeks. Consequently the effect of the 7 mg. thyroxin which the patient had been given May 22 may have begun to wear off about June 10, whereas the 3 mg. given by mouth between June 8 and 10 had hardly become effective. This may explain the sudden increase June 10 of the Bloor I values, from 95 to 145 mg., and the accompanying drop of the split cholesterol to 10 mg. The changes in the chemical composition of the blood may have to be interpreted as the first indication of a deficit in thyroid hormone. The marked and well-known thyroid deficit in myxedema, the low metabolic rate, and the high cholesterol values which occur in the disease seem to support this assumption. The reduction of the cholesterol split products suggests that, aside from its effect on the basal metabolic rate, the thyroid hormone might also further the disintegration of cholesterol by some direct chemical action. Such a direct chemical action has been neither demonstrated nor even investigated, but it might help to explain the comparative rarity of cancer in the thyroid gland. For it is obvious that if the thyroid hormone should affect the disintegration of cholesterol directly, the incitement to cell division caused by cholesterol will be reduced to a minimum where the thyroid hormone is produced, that is, in the thyroid gland. Brailsford Robertson and Burnett have shown, moreover, that changed cholesterol does not further cell proliferation.

Evidence with regard to the direct disintegration of cholesterol by the chemical properties of the thyroid hormone not being available, other factors will have to be taken into account when we endeavor to trace the cause of the sudden and perplexing rise June 10 of the patient's Bloor I cholesterol values. Two factors are worth considering, although they do not furnish conclusive evidence, namely, loss of body-weight involving disintegration of the body fat with resulting liberation of cholesterol and the possibility of an acute, intercurrent, bacterial infection. Aschoff has called attention to the frequent occurrence of cholelithiasis (a disease admitted to represent an accumulation or an increased precipitation of cholesterol) in persons who reduced their weight suddenly by "anti-fat" cures (Entfettungskuren); Rothschild has demonstrated an increase of the blood cholesterol values in starving animals, proportional to the loss of body weight; the analyses of Hueck and Wacker have shown that cholesterol is stored in the fat deposits. A rapid reduction in weight, therefore, such as is known to be produced by ingestion of the thyroid hormone, might have increased the amount of the cholesterol circulating in the blood. But in this instance the patient had lost only four pounds between May 22 and June 10, whereas she lost 17 pounds within the following fortnight (June 10 to June 23), yet the blood cholesterol values dropped during the latter period. Mere loss of weight, therefore, cannot account for the sudden rise June 10 of the Bloor I values, although the subsequent decrease of the blood cholesterol is readily explained by the increase of the metabolic rate to +27 per cent resulting from the daily administration of 0.5 mg. thyroxin from June 10 to June 23.*

* Increase of weight such as occurs in many cases of cancer, from two to five years before the clinical manifestation of the disease, may constitute a measure of defence of the body. I have several such instances in my records. Case 191487 is an illustration. A woman who was five feet in height weighed 180 pounds. The symptoms of which she complained were attributed to overweight and neurasthenia.

The history of the patients does not furnish any clear-cut evidence of acute bacterial infection, but the following entry strongly suggests such a possibility: "June 1, fluid in chest; June 2, fluid in pericardium, increased dulness and displacement to left". Acute bacterial infections tend to increase the blood cholesterol temporarily, whereas low values are found in chronic bacterial diseases. Therefore, the clinical data support the interpretation of the high values June 10 as indicative of a mild or transient attack of pericarditis.

Hemorrhage, ulceration, chronic bacterial infection

Evidence that hemorrhages as well as the less virulent or more chronic types of bacterial infection have a tendency to reduce the Bloor I cholesterol was furnished by the analysis of ninety-five cases of uterine cancer. In the majority of these the cervix alone was involved; they were selected because it was deemed advisable to make a series of observations in cases in which the type and the localisation of the malignant process were practically the same, although in some the condition might be more advanced than in others. Whenever possible blood cholesterol determinations were made before and after radium treatment. Unfortunately, many of the patients were in an excusable hurry to get home and consequently failed to report for the blood test after they had had radium treatment. As a result the number of serial observations is not as large as might be desired. Four successive determinations were made on one patient; three patients had three tests each; fifteen patients were tested twice, but only one blood sample was obtained from each of the other patients.

Our findings in this series were somewhat puzzling from the first. The Bloor I values were much lower than those previously found in carcinoma; "equal" values, with one exception, were conspicuous by their absence. A careful study of

She was told to reduce by diet, and succeeded in losing fifty-three pounds within a year; shortly after, carcinoma of the breast was diagnosed at the Mayo Clinic, although there had been no evidence of malignancy at her first examination, when the dietary measures had been suggested.

the clinical histories revealed, however, that all the patients in this group had two symptoms in common, ulceration and hemorrhage. Although these symptoms might suffice to explain the preponderance of increased values (100 to 140 mg.) the lack of high values (more than 140 mg.) and the comparatively large amounts of cholesterol-split products found in the tests*, several other factors were taken into consideration, such as previous treatment, age, pregnancies, and miscarriages, and the extent of malignant involvement. It seemed possible that a certain parallelism between clinical data and laboratory findings might suggest a clue with regard to the efficiency or the impairment of the organs that regulate cholesterol metabolism. But the data varied so much that it proved impossible to draw any conclusions from them (Tables 1, 2, 3, and 4).

The entire chemical composition of the blood, including its cholesterol content, represents the sum-total of the rate of many metabolic processes, their normality or their abnormality. Under these circumstances it is to be expected that only recent occurrences are likely to influence the cholesterol content of the blood at the time when the determinations were made. Hence, miscarriages, for example, which occurred but a few years before examination in some instances and ten or twenty years before in others could not be shown to have affected the cholesterol values in this series of observations, although they may have had a detrimental effect on the general health of the patient.

It was conceivable that the age factor might be found to influence the cholesterol content of the blood, although metabolic and chemical anomalies were likely to prevail in a group composed entirely of patients suffering from carcinoma. To my disappointment (not unmixed, however, with secret satisfaction, as I had been told on several occasions that the high cholesterol values in carcinoma were merely due to the age of the patient and were consequently without bearing on the nature of the disease) the analysis of the histories failed to re-

* Numerous observations had shown that inflammatory or ulcerative processes are accompanied by increased Bloor I values and marked differences between the values of the Bloor I and II tests.

Table 1

CARCINOMA OF CERVIX

Cases with normal cholesterol values (70 mg. to 100 mg.) before radium

	Case	Tests	Age	Civil state	Blood cholesterol values (mg. per 100 c.c. whole blood) Date 1918	Bloor I	Bloor II	Difference	Microscopic Diagnosis	Ulcerating	Hemorrhage	Previous treatment	Size of growth	Pregnancies	Miscarriages
A	1. 228642		43	M	5-7	100	111	11	•	0	Recent	Cautery 2-18		4	1
	2. 246946		61	M	9-28	99	133	34	0	0	Yes	0		6	0
	3. 228736		57	M	4-26	98	111	13	0	0	Yes	Subtotal hysterectomy 28 mos. ago		7	1 abortion
	4. 240391		44	S	8-1	94	148	54	0	0	Profuse	0		0	0
	5. 225241		31	M	9-25	95	121	26	0	Yes	Yes	Cautery 10-17		0	0
	6. 227701		42	M	4-17	89	103	14	0 Inop.	0	0	0		6	0
	7. 228309		50	M	4-19	83	133	50	0 Inop.	0	Severe	0		4	1
	8. 230969		48	M	5-13	83	95	12	0	0	0	0		0••	0
	9. 248447		55	M	10-14	74	111	37	0	0	Slight	0		5	0
	10. 215144		28	M	11-21	67	92	25	0	Yes	Yes	Cautery 2; hysterectomy 18 mos. ago		3	0 Tumor diagnosed 3 mos. after birth of twins
B	Cases with normal cholesterol values (70 mg. to 100 mg.) after radium														
	1. 239769		41	M	7-27	96	133	37	6	0	Slight	0		4	1
	2. 206350	1	47	M	1-5	95	121	26	0	0	Yes	0		9	1 18 mos. before. After 2 mos. patient began to bleed and has bled ever since.
	3. 108715		43	M	12-20	95	136	41	Yes	0	0	Operations within 18 mos.		5	0 Removed gallbladder, many stones, fibrous cervix, right parovarian cyst, ovary and tube. Hysterectomy, ovarectomy, appendectomy, 7-2-14.
	4. 230969		48	M	6-1	95	111	16	0	0	0	0		0••	0
	5. 206350	2	47	M	8-29	93	133	40	0	0	Yes	0		9	1 18 mos. before. After 2 mos. patient began to bleed and has bled ever since.

Table 1 continued

6. 244919	50	M	8-21	95	191	98	0	Yes	0	Cautery 5-2 and 5-7		2	0
7. 216949	41	M	5-8	89	102	13	0	Yes	Yes	Hemorrhoidectomy		1	0
8. 245026	61	M	12-5	67	76	9	0	0	Yes	0	Exten- sive	3	1
C													
Cases with high cholesterol values (140 mg. to 200 mg.) before radium													
1. 249774	55	M	10-31	156	212	58	Epithel.	0	Little	0		1	1
2. 246382	60	M	9-24	148	188	40	0	Slight	Slight	0		5	1 abortion
3. 244959	54	M	9-11	145	171	26	0	0	Slight	Laparotomy 7-10-17		0	0
4. 246310	69	M	9-14	144	171	27	0	Yes	Yes	0		3	0
5. 245026	61	M	9-11	140	171	31	0	0	Yes	0	Exten- sive	3	1
D													
Cases with high cholesterol values (140 mg. to 200 mg.) after radium													
1. 217144	48	M	9-11	148	183	35	Epithel.	Yes	0	Curettage showing squamous-cell epi- thelioma; vaginal hysterectomy 12-27-17		1	0
2. 198518	43	M	6-5	146	177	31	Epithel.	0	Slight	Cautery 6 mos. before		0	0
3. 199086	41	M	10-9	145	200	55	0	0	Leukorrhea; wears nap- kin con- stantly	Tumor of uterus; partial hyster- ectomy, 1912		0	0 Wants children

* Elsewhere

** Used no preventive

Table 2.

CARCINOMA OF THE CERVIX

Cases with increased cholesterol values (100 mg. to 140 mg.) before radium

Case	Tests	Age	Civil state	Blood cholesterol values (mg. per 100 c.c. whole blood) Date 1918	Floor I	Floor II	Difference	Microscopic diagnosis	Ulcerating	Hemorrhage	Previous treatment	Size of growth	Pregnancies	Miscarriages
1. 245733		47	M	9-20	138	173	35	0	0	Yes	0		5	3 seemed to follow last labor 3 yrs. before
2. 249923		38	S	10-31	136	155	20	0	Yes	Yes	0		0	0
3. 232375		38	M	5-28	133	200	67	0	Yes	Yes	Continuous diarrhea		2	0
4. 228642	4	43	M	10-5	132	177	45	*	0	0	Cautery 2-18; tissue reported adeno-carcinoma		4	1
5. 190066		41	M	5-30	132	148	16	0	0	Leukorrhea; wears napkin constantly	Tumor of uterus, 1912; partial hysterectomy, October, 1912		0	0 Wants children
6. 247005		60	M	9-30	129	183	54	0	0	Excessive	0		5	1 at 3 mos. cause: lifting(?)
7. 244772		42	M	9-16	129	159	30	Epith. of uterus; marked fibrous and lymphatic infiltration. Bilateral hydro-salpinx.		Slight	Cautery 4 weeks before		1	3
8. 250775		53	M	11-15	127	164	37	0	0	Yes	Perineorrhaphy, April, June, and Aug., 1918 curettement. Cervix cauterized Aug., 1918		0	0
9. 247015		60	M	10-2	123	160	37	Epithelioma	0	Yes	1915 Appendectomy, ovarectomy, pus tubes. Lesions of genitalia 22 years before		5	1

Table 2 continued.

10. 83149		42	M	6-1	131	146	25	0	0	0	Gallstones, uterine fibroids, jaundice and diabetes		6 2 born dead	1
11. 229045		35	M	4-27	121	144	23	0	0	Yes	April, 1918 cautery		0	Abortion 2 or 3 mos. after marriage
12. 234156		42	M	6-18	120	159	39		0	Yes	Yes		0	0
13. 244319		50	M	9-6	118	157	39	0	0	Some	Cautery to cervix and vagina		2	0
14. 251191		46	M	11-22	118	154	36	0	Yes	Yes	Malignant growth on tongue 3 yrs. before; microscopic exam.		1	1
15. 244525		50	M	9-9	117	140	23	0	Yes	Slight	0	Extensive	0**	0
16. 243327		55	M	8-26	117	167	50	0	Yes	Severe	Consultant's resume: Cancer of cervix extending to posterior vaginal wall.	Extensive	6	2
17. 237866		63	M	7-11	117	167	50	0	Consultant's resume: Large cancer of cervix		0		8	0
18. 232474		66	M	5-29	113	148	35	0	Since cautery	Yes	Cautery to cervix 2 weeks before		4	1
19. 213883		55	M	11-24 1917	111	148	37	Polypoid endometritis	0	Leukorrhea	Fibroids removed 7 or 8 years before		11	2 Last 15 years before
20. 228642	1	43	M	4-24	111	140	29	*	0	Slight	Feb., 1918 cautery. Tissue reported adenocarcinoma		4	1
21. 228642	3	43	M	4-24	110	126	16	*	0	Slight	Feb., 1918 cautery. Tissue reported adenocarcinoma		4	1
22. 246259		61	M	9-26	107	127	27	0	Profuse	Slight	0		10	1 abortion 29 years before
23. 246095		46	M	9-21	104	163	59	0	0	Profuse	0		1	2 Last (8 mos., dead some time) 3½ yrs. before

Table 2 continued

24. 239430		57	M	7-25	102	150	46	0	Yes	Yes	0		5	1
25. 225391		42	M	3-23	102	148	46	0	Very slight	Yes	Cautery on uterus 2 years before		9	0
26. 132514		58	M	3-8	102	116	14	Epithelioma	Yes	0	Tumor from vulva and inguinal glands		1	1 At 1 month.

* Elsewhere.
** Used no preventive.

Table 3.
CARCINOMA OF THE CERVIX
Cases with increased cholesterol values (100 mg. to 140 mg.) after radium

Case	Tests	Age	Civil state	Blood cholesterol values (mg. per 100 c.c. whole blood) Date 1918	Bloor I	Bloor II	Difference	Microscopic diagnosis	Ulcerating	Hemorrhage	Previous treatment	Pregnancies	Miscarriages
1. 240108		59	M	11-1	138	168	30	Uterus, epith. of cervix	Yes	Yes	Perineorrhaphy; operation for rectal fissure	2	0
2. 221242	1	47	M	9-5	136	164	28	0	0	0	0	7 1 instrumental	2 abortions
3. 199666	1	63	M	4-11	135	167	32	0	0	Very slight	0	9	0
4. 203610		56	M	1-5	133	167	34	0	Yes	Slight	0	0	1 at 5 mos.
5. 202077	1	34	M	9-23	133	164	31	Epithelioma	0	0	Curettement Dec., 1916	2	7 all under 7 mos.
6. 246382	2	60	M	10-8	132	169	37	0	0	Yes	0	5	1 abortion
7. 229046	2	36	M	5-8	131	136	5	0	0	Yes	Cautery 4-18	0	1 abortion 2 or 3 mos. after marriage
8. 226652		39	M	7-31	129	163	34	Large fungating malignant mass protruding from cervix; inop.	0	Yes	Hysterectomy 5 years before	1	0
9. 241522		45	M	10-17	139	159	30	0	0	Slight	0	2	0
10. 245601		42	M	10-7	128	159	31	Epithelioma	Yes	Occasional	Appendectomy 14 years before*; abscessed tube, both ovaries and tubes removed, time not given*	1	0
11. 228736		57	M	6-29	128	142	14	0	0	Yes	Subtotal hysterectomy 28 months before	7	1 abortion
12. 238347		67	M	7-22	127	154	27	0	0	Yes	Hysterectomy*, radium*, injury to hip 3 yrs. before, fell on sidewalk, 2 yrs. to heal	4	0

Table 3 continued

13.	197966		26	M	11-1	127	138	11	Epithelioma	0	Yes	Curetted 5 yrs. before, after miscarriage	1	1 5 yrs. before, at 7 wks.
14.	235385		46	M	10-8	126	150	24	0	Yes	Severe	0	2 still births	0
15.	244059		54	M	9-25	126	155	29	0	0	Yes	Laparotomy 7-10-17	0	0
16.	207000	2	67	M	9-6	126	163	37	0	Yes	Yes	0	1, 1 child died in infancy	0
17.	199666	2	63	M	4-17	125	167	42	0	0	Very slight	0	3	0
18.	229046	3	35	M	9-30	123	152	29	0	0	Yes	Cautery 4-18	0	1 abortion 2 or 3 mos. after marriage
19.	237297		59	M	7-24	123	154	31	Adenocarcinoma		Profuse year before	Had diarrhea one summer; cured by castor oil daily	3	0
20.	246733	2	47	M	10-3	123	150	27	0	0	Yes	0	5	3 Trouble seemed to follow last labor
21.	153246	1	68	M	11-23 1917				Uterus; carcinomatous involvement. Tubes: Bilat. chronic salpingitis. Ovaries: Bilat. carcinomatous papillary cyst		Sometimes bad	Hemorrhoids, 1916; curettage at Chicago	1 child not right mentally	1
22.	207000	1	67	M	1-3	121	191	70	0	Yes	Yes	0	1	1
23.	220667		49	M	5-28	121	138	18	0	0	Yes	Cautery 12-11-17	4	0
24.	161069		55	M	11-24	121	148	27	0	Yes	Yes	0	9	14 yrs. before following pregnancies
25.	206350	3	47	M	9-12	120	167	47	0	0	Yes	2 mos. after miscarriage patient began to bleed and bled ever since	9	1 1½ yrs. before
26.	226626		30	M	4-26	116	116	0	Inop. cancer	0	0	Operation in Pittsburgh 8 mos. before. Unable to speak English	0	0
27.	253532		49	M	12-11	116	146	30	0	Yes	Yes	0	3	0

Table 3 continued

28. 218959		53	M	4-10	116	142	26	0	0	Yes	0	4	2
29. 236404		67	M	10-12	116	140	24	0	Yes	Profuse	0	6	0
30. 221242	2	47	M	9-14	115	155	40	0	0	0	0	7 1 instrumental	2 abortions accidental
31. 245733	3	47	M	10-4	115	142	27	0	0	Yes	0	5	3 Trouble seemed to follow last labor
32. 227791	2	42	M	8-15	115	142	27	Inop. cancer	0	Yes	Tubercular left cervical gland 9 years before	6	0
33. 246946	2	61	M	12-20	114	136	22	0	0	Yes	0	6	0
34. 245259	2	61	M	10-7	114	128	14	0	Yes	Yes	0	10	1 abortion
35. 225219		63	M	6-28	111	167	56	Inop. carcinoma of the cervix	0	Yes	0	2	0
36. 212785		49	M	5-25	111	132	21	0	Yes	Yes	0	0	0
37. 202955	1	33	M	4-2	111	127	16		0	Yes	0	2	1
38. 202077	2	34	M	10-4	104	138	34	Epithelioma	0	0	Curettement December, 1915	2	7 All under 4 months.
39. 153240	2	68	M	7-31	102	155	53	(See Case 21 this table)	0	Sometimes bad	0	1	1
40. 225391	2	42	M	8-5	102	120	18	0	Very slight	Yes	Cautery on uterus 2 yrs. before	9	0
41. 244625	2	60	M	9-23	102	121	19	Extensive Ca. with destruction of lip of cervix leaving opening into fundus		Yes	0	0**	0
42. 232474	2	55	M	6-19	102	148	46	0	Since cautery	Yes	Cautery to cervix 2 weeks before	4	1

* Elsewhere

** Used no preventive

Table 4

THE INFLUENCE OF ULCERATION AND HEMORRHAGE ON THE BLOOD CHOLESTEROL VALUES IN NINETY-FIVE CASES OF CARCINOMA OF THE CERVIX, BEFORE AND AFTER RADIUM TREATMENT

High Bloor I values: above 140 mg.	Cases	Ulceration	Hemorrhage
Group I - before radium treatment	5	2	5
Group Ia - after radium treatment	3	1	1
Increased Bloor I values: 100-140 mg.			
Group II - before radium treatment	26	11	19
Group IIa - after radium treatment	42	16	37
Normal Bloor I values: 70-100 mg.			
Group III - before radium treatment	10	2	8
Group IIIa - after radium treatment	8	1	1

Table 5

ABSENCE OF RELATION BETWEEN AGE AD BLOOD CHOLESTEROL VALUES IN

NINETY-FIVE CASES OF CARCINOMA OF THE CERVIX

High Bloor I values: above 140 mg.	Cases	Average age	Oldest patient	Youngest patient
Group I - before radium treatment	5	58.6 years	63 years	54 years
Group Ia - after radium treatment	3	44.0 years	48 years	41 years
Increased Bloor I values: 100-140 mg.				
Group II - before radium treatment	26	48.6 years	63 years	35 years
Group IIa - after radium treatment	42	68.0 years	68 years	26 years
Normal Bloor I values: 70-100 mg.				
Group III - before radium treatment	10	45.9 years	57 years	28 years
Group IIIa - after radium treatment	8	47.2 years	51 years	41 years

veal any relation between the age of the patients and their blood cholesterol values (Table 5). Metabolic, perhaps endocrine, disturbances may, therefore, be said to influence the blood cholesterol values far more than the actual age of the patient.

The effect of ulceration and hemorrhage, symptoms of recent occurrence in our series and as such likely to change the chemical composition of the blood, may be seen in Table 4. The findings correspond with those reported in Study V. There is a reduction in the number of patients having high values after radium treatment, and the majority of the patients have increased values, such as accompany inflammatory reactions after exposure to radium. But whereas high values had been found to prevail only before radium treatment in the series reported in Study V, the group of patients under discussion shows a marked preponderance of increased (inflammatory) values before and after radium treatment. The series in Study V was composed chiefly of nonulcerating, nonbleeding types of carcinoma, and included a very small percentage of gastric cancers; in the later series a history of ulceration is found in approximately one third of all the cases, and hemorrhages are reported in every case. It would seem as if the severity of the hemorrhage especially affects the blood cholesterol values. The five patients having high values before radium treatment (Group C, Table 1) gave a history of hemorrhage, but the loss of blood was described as "slight", whereas it is characterised as "severe", "profuse", or "recent" in the group of patients who had normal values before radium treatment (Group A, Table I). In Group IIa (increased values after radium treatment) one patient giving a history of hemorrhages as well as of "ulcerative destruction of the cervix, leaving an opening in the fundus", was found to have practically normal Bloor I values.

The foregoing observations point to a reduction of the pure cholesterol (Bloor I) with an accompanying increase of the changed cholesterol by ulceration and hemorrhage. Cautery appears to have the same effect, for in a number of cases not belonging to this series similar changes in the chemical composition of the blood were found after the use of cautery for malignant conditions, and frequent reference is made to this mode of treatment in Tables 1, 2, and 3. The following explanation seems admissable: ulcerative processes are known to be accompanied by a rise of body temperature, while the latter is admitted to represent an acceleration of metabolism. If, as I have shown, the increase of the metabolic rate tends to reduce the Bloor I values and to increase the cholesterol-split products, the changes in the blood chemistry following ulceration may also simply be the result of a more rapid rate of basal metabolism.

As far as I could ascertain the effect of hemorrhage on the metabolic rate has not been studied. It does not seem improbable, however, that loss of blood and the resulting endeavors of the organism to make good the loss will lead to greater metabolic activity, thus causing an increase of the basal metabolic rate. The fact that the elimination of tumor grafts in resistant animals is brought about by ulceration and hemorrhage (Woglom, Bashford, Murray, Cramer) suggests that both ulceration and hemorrhage represent means by which the organism strives to rid itself of neoplastic growth. The reduction of tumor growth, moreover, would undoubtedly be furthered by the changes in the chemical composition of the blood such as are found to accompany ulceration and hemorrhage, whether these changes be due entirely to increased metabolism or to other as yet unknown factors.

Blood cholesterol determinations furnish valuable information, but they do not in themselves reveal the extent of malignant invasion. The cholesterol test is not a diagnostic test; this cannot be emphasized too strongly. Nevertheless, in conjunction with other data the cholesterol content of the blood may be expected to indicate the amount of fight which the patient is putting up against malignant invasion. Serial, routine observations on one patient are, consequently, of far greater value than even a large number of single observations on different patients; the former keep us informed of the effect of therapeutic measures and often herald coming danger; the latter merely give an instantaneous picture of the chemical conditions prevailing in the blood at the time the determination is made, interpretation of which may be rendered extremely difficult by the cumulative effect of many unknown factors. The increase of the Bloor I values accompanied by a decrease of the cholesterol-split products suggested unfavorable developments for a patient suffering from sarcoma of the pelvis (Case 199185), on whom serial observations were being made, even before the patient had had occasion to complain of an exacerbation in his condition, which became clinically patent a few weeks later.

The following case is a striking illustration of the value of serial determinations, and gives, moreover, valuable information concerning factors that influence the chemical composition of the blood.

Recurrent carcinoma of the breast complicated by pregnancy. Case 171479. A woman who was married at the age of twenty suffered from a recurrent carcinoma on the sternum at the age of twenty-six, two years after amputation of the left breast (Halsted operation). Her history, summarized in Table 6, contains interesting data with regard to the relation between thyroid activity, pregnancy, and the development of malignant growth. It is known that pregnancy exerts a marked influence on the activity of the thyroid gland. The effect of the thyroid hormone on the cholesterol content of the blood has already been discussed. The clinical data in the history of this patient strongly suggest that a not fully efficient thyroid gland was overtaxed by repeated pregnancies and that the mismanagement of cholesterol metabolism resulting from thyroid deficiency greatly furthered the development of neoplastic growth.

Three strikingly opposed views of the effects of pregnancy on malignant growth may be found in the literature. Moreau and Herzog found that in experimental animals gestation accelerated the evolution of tumors; Haaland, on the contrary, noticed that pregnancy had an inhibitory influence; according to Uhlenhuth

Table 6

DATA SUGGESTING A RELATION BETWEEN THYROID INSUFFICIENCY, MENSTRUATION, PREGNANCIES AND THE MANIFESTATIONS OF MALIGNANCY IN THE HISTORY OF CASE 171479

Menstrual history	Thyroid activity	Pregnancies	Malignancy
1903 at age of 11 menses appeared, regular, profuse, eight to nine day type			
	1908 at age of 16 goiter developed, affected voice at time and prevented wearing a collar		
		1. April, 1913 normal delivery	
		2. April, 1915 normal delivery	
	June, 1916 goiter disappeared completely after Halsted amputation. Sept., 1916 goiter reappeared and enlarged, causing nervousness and insomnia. Sept. 8, 1916 diagnosis: palpable thyroid; small adenoma	3. Autumn, 1916 early miscarriage	Oct., 1915 nodule in left breast first noticed and ascribed to nursing. June, 1916 Halsted amputation of left breast
May, 1917 after miscarriage constant flow until July; controlled by second curettage		4. May, 1917 "Six-weeks" miscarriage	Jan., 1917 excision of nodule of right breast. May, 1917 "Piercing of blood-cyst" in scar of left breast. May, 1917 mass on sternum noticed. Aug., 1917 excision of mass on sternum about "the size of a hen's egg". Aug., 1917 to Jan., 1918, radium treatment 16,850 mg. hours. Dec., 1917 cautery twice of recurrence on sternum.
	Feb., 1918 to June, 1918 small doses of thyroxin at irregular intervals. No enlargement of thyroid trouble during fifth pregnancy	5. June 29, 1918 normal delivery of 5-pound baby.	Oct. 14, 1918, cause of death in necropsy report: Spanish influenza.

and Wiedans it even resulted in spontaneous regression, whereas Albrecht and Hecht came to the conclusion that pregnancy had no influence on the establishment and growth of tumors. Recently Slye has been able to show that in mice the size of the tumors is kept down and the longevity of the animals increased by a rapid and continuous succession of pregnancies. Clinical observations furnish a similar diversity of conclusions, but Slye explains this diversity by the "hiatus" between human pregnancies that was not allowed to occur in the mice used in her experiments.

The question presents itself whether in individual cases the relative efficiency of one of the glands of internal secretion might not help to account for these contradictory findings. The thyroid is known to be activated by pregnancy; a thyroid gland capable of responding by greatly increased activity might be one of the factors responsible for the retrogression of tumors during pregnancy, whereas a less efficient thyroid might just be able to meet the demands, leaving the tumor unaffected, and an inefficient gland would allow the neoplastic tendency to get the upper hand. It is probable that the last assumption explains the progress of malignancy in our patient: the clinical data contain evidence of disturbances of the thyroid function, and every gestation, with the exception of the first, appears to have caused a flare-up of the neoplastic tendencies. Malignancy first developed in the left breast five months after the birth of the second child, April, 1915. A nodule (referred to as "cyst") appeared in the right breast shortly after an early miscarriage in the autumn of 1916 and had to be excised in January, 1917; in May, 1917, a six weeks' miscarriage was followed almost immediately by a recurrence on the sternum. The goiter which had developed at the age of sixteen had only disappeared completely after amputation of the breast to reappear and become troublesome again in September, 1916, presumably as a pregnancy goiter in connection with the first miscarriage. The data relative to the thyroid suggest a certain inefficiency of the gland and attempts at compensatory hypertrophy. This interpretation is also supported by the fact that during the fifth pregnancy the thyroid did not enlarge or give any trouble when small doses of the thyroid hormone were being given at intervals from the fifth month until delivery.

Whether the profuse and prolonged type of menstruation (eight to nine days) should also be looked on as evidence of thyroid hypo-activity seems uncertain. Allen Starr, Kirk, Schotten and others consider a tendency to menorrhagia characteristic of hypothyroidism and myxedema; amenorrhea, on the other hand, is referred to by Biedl as "one of the earliest symptoms of Grave's disease". But Osborne takes the opposite view and connects amenorrhea with subnormal activity of the thyroid gland, and profuse menstruation with hyperthyroidism. In order to obtain data that would support at least one of these two conflicting opinions, I made a careful analysis of the clinical histories of thirty-five cases of exophthalmic goiter with high basal metabolic rates and of twenty-five cases of myxedema in which the rates were far below normal. The result was disappointing; profuse and scanty menses were recorded with almost equal frequency in both hyperthyroidism and hypothyroidism. Thinking that perhaps a very much larger series of observations might be required, I asked Dr. H. S. Plummer's opinion on the subject; he informed me that the data which he had collected so far did not justify definite conclusions. The vague and varying interpretations of the terms "scanty" and "profuse" by the patients undoubtedly has added no little to the difficulty of obtaining conclusive data; one patient considers menses profuse, which another would look on as normal or scanty.

I have called attention to the fact that a reduction of the Bloor I cholesterol values follows both radium treatment and the administration of the thyroid hormone, and have suggested that the effect of radium on the chemical composition of the blood may be due either to the photo-activity of radium or to the stimulation of the metabolic processes by radiotherapy. The basal metabolic rate is admittedly controlled by the functional activity of the thyroid, if not exclusively, at any rate to a great extent, and the thyroid has been called the "pacemaker of the body" (Crile). It is obvious, however, that a functionally inferior gland will not only work half-heartedly under ordinary conditions, but may even fail to respond to stimulation. If the effect of radium treatment on the blood cholesterol values should prove to be the result of increased thyroid activity, rather than of photo-dissociation, we might expect to get little response to radium treatment in cases in which the functional activity of the thyroid gland was somewhat impaired.

A striking lack of response to radiotherapy was observed in the patient with recurrent carcinoma of the breast. The treatment seemed to have little or no curative effect on the tumor (Figs. 15, 16, and 17), and did not appear to produce the changes in the blood cholesterol values that I had found associated with the improvement of malignant conditions.

The first blood cholesterol determination, Nov. 24, 1917 (Fig.18), showed moderately increased Bloor I values, possibly to be explained by the ulcerative type of the growth, and an extremely small amount (5 mg.) of cholesterol-split products. As 7750 mg. hours of exposure had already been given, the chemical composition of the blood made me fear a bad prognosis, although I had not yet seen the patient. Radium treatment was continued. In February, 1918, the patient's condition was pronounced to be hopeless and she was not expected to live more than six weeks or two months. She then had had in all 16850 mg. hours of radium treatment. Her blood cholesterol determination gave equal values, notwithstanding prolonged radiotherapy. The clinicians, knowing that I believed in the possibility of the human body waging a winning battle against cancer, a belief founded on the spontaneous retrogression of tumors observed in well authenticated cases sent the patient to me, in the hope that my convictions might at any rate cheer her up a little. She was in the fifth month of pregnancy, and greatly depressed by anxiety about the fate of her two living children in the event of her death. During my conversation with her, I was impressed by her clear-sighted estimate of the gravity of her condition and by her determination to fight the disease for the sake of her children. She was the daughter of Canadian pioneers and had lived a life which furnished little opportunity for coming in contact with the problems of scientific research; nevertheless her quick appreciation of the difficulties and the possibilities in such work was surprising. Her intelligent cooperation, her cheerfulness, and her pluck were to fill us all with admiration during the months that followed.

Having explained to her my reasons for believing that in cases of carcinoma the body might be compared to a poorly burning fire, I also told her how my investigations seemed to show that radium "fanned" the fire, making it burn more brightly. But "fanning" a fire was not the only means at our command to quicken a flame: We could often attain this end by using very combustible fuel. As she had shown little response to radium treatment, we might still try what could be done by the use of fuel that is easily consumed. It had been found that a milk-diet, by furthering the elimination of waste products and by furnishing a type of food easily digested, had improved many conditions in which the body functions were carried on in a half-hearted way. A milk diet might, therefore, assist her body in combating the disease, although I could give her no definite promise of success. But if other human bodies had succeeded in winning the battle, although their condition, too, had been inoperable and apparently hopeless, there seemed to be no reason why her body should not succeed to the same extent. She gladly consented to give my suggestion a trial.

The milk treatment consisting of complete rest in bed, and milk as exclusive diet was taken in a sanatorium. After four weeks the milk began to be repugnant. During this time the patient was given small doses of the thyroid hormone (1.75 mg. in all). A decided improvement could be observed in her general condition as well as in the blood cholesterol values. She gained 25 pounds. This increase can hardly be ascribed entirely to the progress of gestation. The blood hemoglobin rose to 70 per cent. The amount of cholesterol-split products had become satisfactory but it diminished as soon as the ordinary mixed diet was resumed (March 28, 1917). It was deemed advisable, under these conditions, to increase the dose of thyroxin; 4 mg. were given between March 28 and April 9. Again the cholesterol values improved. During the following weeks the patient had a severe attack of grippe, and it was considered wise to give her an injection of Dr. Rosenow's pneumococcus vaccine because in several pregnant women the grippe had developed into fatal pneumonia. Administration of the vaccine was followed by an increase of the Bloor I cholesterol values. Whether this rise was due to the therapeutic measure or to the acute bacterial infection was uncertain at the time; later observations during the influenza epidemic, 1918 and 1919, showed, however, that some connection exists between measures calculated to increase the immunity against bacterial infection and the change in the cholesterol content of the blood. This point will be discussed in Chapter X.

Shortly after the administration of the vaccine, the cholesterol values having been found to increase and the tumor to assume an angry appearance, it was decided once more to try the effect of radium. April 25, an exposure of 1200 mg. hours was given after the blood cholesterol had been determined, and a second cholesterol determination was made five days later; the drop of the Bloor I values and the increase of the split cholesterol, which had been observed in other cases, may be seen in Figure 18, in which the radium treatment is indicated by "R". The diagram shows that each successive exposure to radium (each letter "R" represents from 1200 mg. hours to 1900 mg. hours) was followed by the changes in the blood cholesterol values already described. Whether this response to radiotherapy, which had been lacking in our earlier observations, was the result of the continued administration of the thyroid hormone (0.5 mg. was given May 20, 0.5 mg. daily from May 22 to 25, and 1 mg. May 29) is hard to decide. Few therapeutic measures, except surgical procedures perhaps, give results that would justify a conclusive and catagorical post hoc, propter hoc; and many drugs even, of which the physiologic action seemed established beyond doubt, have been known to fail in individual cases. But at the beginning of June, 1918, the patient was holding her own to an extent which her condition in February had given little reason to expect, and the blood cholesterol values seemed to show with how much success she was fighting the disease. However, the consistently low lymphoid defence, under twenty, made me feel apprehensive about the ultimate success of the battle. Various observations, to be mentioned later, had confirmed the importance of the lymphocytic response to which I called attention in Studies on cholesterol IV; patients whose lymphoid defence did not show much increase after radium treatment or other therapeutic measures did not seem to do as well as those in whom the percentage of small and large lymphocytes combined remained between 30 and 40.

In consideration of the fact that pregnancy was nearing full term, radium treatment was suspended after June 17. But 2 mg. of thyroxin were given June 19 and 0.25 mg. June 27. Confinement took place June 29 at the Stanley Hospital; delivery was normal and rapid. The baby, a girl, weighed five pounds and though small was perfectly formed. A brief outline of the child's subsequent history may be of interest because of the unusually adverse conditions under which its prenatal development took place and because in the only similar case on record the history of the child could not be traced (Bainbridge). Since the mother's condition precluded nursing, artificial feeding had to be resorted to. No less than seven feeding formulas had to be tried. Six of these could not be retained by the infant and it lost weight till it had come down to 3.75 pounds. Finally the seventh formula (protein milk mixed with buttermilk) used by Dr. Taylor gave satisfactory results. The infant gained steadily, though at ten weeks of age it weighed only eight pounds. Until this time the baby had been taken care of at the Stanley Hospital. Special circumstances made it impossible for the mother to procure the protein milk on which alone it seemed to thrive. Consequently a friend of the mother took charge of the baby and it is due entirely to the care which she received at the hands of this friend that she developed into a normal average baby. The child's picture, taken at twelve months, speaks for itself (Fig. 19). The baby began to walk and talk at the age of nineteen months, and showed evidence of a good average intelligence and of a sunny disposition (Fig. 20). Dentition was normal, perhaps slightly delayed. The teeth appeared in the usual order, central incisors, lateral incisors, anterior molars. The latter were all out within four weeks during the eighteenth month. Figure 21 shows the child at the age of four years.

The mother regained her strength slowly after delivery. She had a slight increase in temperature for several days (100° to 101°). The tumor drained profusely. The pregnancy-leukocytosis (June 18) and the temperature and drainage probably account for the low Bloor I values and the relatively large amount of split cholesterol found July 10. The patient returned to her temporary home in Rochester and was able to walk to the Clinic daily - a distance of five blocks - to have the tumor dressed. The house where she lived was near the railway and constantly exposed to the smoke of passing trains and side-tracked engines. Although unavoidable, the latter fact may have been detrimental to her for reasons to be discussed in connection with the relation of the combustion products of fuel to the incidence of malignant disease.

Shortly afterward I was obliged to leave Rochester for several weeks and thereby was prevented from continuing my observations on this case. On my return towards the end of September, the patient's condition made it very doubtful whether the brave fight she was making against the disease could be turned into a victory. No visible increase of malignant tissue could be detected outwardly, however; there had been some hemorrhages from the tumor, which was draining profusely. The patient had lost strength and weight but none of her determination to "carry on" for the sake of her children. October 2 she suddenly developed symptoms suggestive of bronchopneumonia and died ten days later. The "Spanish influenza" was beginning to appear in epidemic form at the time, but the possibility of involvement of the lungs by the malignant process was also to be considered.

At necropsy no malignant invasion of the lungs could be detected, either macroscopically or microscopically, but there was evidence of lobar pneumonia (which is characterised in the necropsy report as "probably Spanish influenza"), and thrombosis of the pulmonary artery, with resulting infarction. The malignant process was found to involve the sternum, the anterior chest wall, the right mammary gland, and apparently the right and left axillary glands, but microscopic examination failed to reveal any carcinoma in the latter. Sections of the growth on the sternum and of the right breast showed extensive fibrosis, hyaline degeneration, and carcinomatous involvement with extensive necrosis; because of the latter the sections stained very poorly. The liver showed complete fatty degeneration and contained two metastatic areas 1 cm. and 2 cm. in diameter respectively. Histologically, the malpighian corpuscles of the spleen were found to be atrophic: This observation is interesting in connection with the persistent low lymphoid defence previously mentioned, and seems to support the view which connects resistance to malignant growth with the integrity and the functional activity of the lymphoid tissues. The adrenals and pancreas were normal microscopically. Some of the other findings, such as fatty degeneration of the heart muscle and "moderate fatty changes with cloudy swelling" of the kidneys, were to be expected in view of the ulcerating tumor and the terminal pneumonia.

Through a regrettable misunderstanding I was not present at the necropsy and failed to secure the thyroid gland; the latter is not removed as a routine procedure at necropsies. Microscopic examination of the gland might have furnished evidence in support of my deductions as to its impairment. Lorand has reported that he found the thyroid atrophic in carcinoma. However, even in typical cases of myxedema the histologic changes have been found to be out of all proportion to the physiologic inactivity of the gland (Biedl, Falta, Vincent) and the same lack of microscopic evidence has often been observed with regard to the pancreas in diabetes (Joslin, McCallum).

This case has been reported in detail for the following reasons: (1) The necropsy findings show that death was not due primarily to the malignant process, but to an acute intercurrent bacterial infection, against which a weakened organism had no chance of victory; (2) the histologic picture of the malignant growth furnishes evidence of the body's endeavors to combat the neoplasm; fibrosis, hyaline degeneration and necrosis are known to accompany the recession of malignant growths, whether spontaneous or the result of radium treatment; it is still a matter of debate whether the proliferation of the fibrous tissue or the destruction of the neoplastic cells is the primary factor (Doederlein, Aschoff, Wood). (3) The blood cholesterol values proved an indication of the fight made by the body, cholesterol metabolism being at its lowest when the patient was not expected to live more than two months; evidence of a more active cholesterol metabolism was found while she was holding her own far beyond expectation. But it is impossible to say whether this activation of the cholesterol metabolism was due to the tardy effects of radium treatment, to the inflammatory reaction connected with the breaking down of the tumor, to gestation, or to the administration of the thyroid hormone, since each of these factors seems capable of increasing the basal metabolic rate. (4) Malignancy first developed six months after the second normal delivery; it was notably aggravated by two subsequent miscarriages. No thyroid hormone was given at that time. The fifth pregnancy was carried to full term; thyroxin was administered from the fifth month of gestation until shortly before delivery, and malignancy appeared to be held in check and to retrogress, rather than to progress. All these facts seem to support the opinion of those who hold that the surplus of cholesterol found in the blood in normal pregnancies (Aschoff, Autenrieth and Funk, Bacmeister and Havers) furthers the multiplication of the cells of the fetus; that in the event of a miscarriage this surplus might promote the proliferation of other cells (malignant proliferation) is obvious; they also suggest, however, that in this instance the thyroid hormone in some way assisted the utilisation of the cholesterol by the fetus during the fifth pregnancy, and that consequently the tumor cells were put on short rations, which impeded their multiplication and resulted in necrotic destruction of areas in the tumor.

The multiplicity of factors involved in this case forbids definite conclusions, but the patient lived far longer than her condition seemed to warrant, gave birth to an apparently healthy child, and died of an intercurrent infection. It remains a matter of conjecture whether in the end had no epidemic of influenza intervened, she could have overcome the malignant neoplasia, like the patient whose inoperable and hopeless condition is described by Rohdenburg. But, at any rate, her history furnishes a striking illustration of the extent to which the human body can hold its own against malignancy.

<u>The blood cholesterol values and the menstrual cycle.</u> A factor which might reasonably be expected to influence the blood cholesterol values in women is the menstrual period. However, during about 2,000 determinations made between 1915 and 1920 I did not find evidence that menstruation affects the blood cholesterol values to any appreciable extent as compared with the influence of many other factors such as the diet, bacterial diseases, ulceration, severe haemorrhages such as occur in cancer of the uterus and radiotherapy; nor did numerous blood cholesterol curves show cyclic variations which seemed referable to the menstrual cycle. These findings suggest that although the gonads doubtless influence metabolic processes, the ovaries do not play as important a part in cholesterol metabolism as, for example, the suprarenals, the thyroid, the liver and possibly the pituitary or the pancreas.

Since Chauffard (1917) reported cyclic changes in the blood cholesterol which he attributes to the influence of the corpus luteum, it seemed advisable to make serial observations on the effect of menstruation by Bloor's two methods, which were not used by Gonalons, whom Chauffard quotes. Serial observations were made on two women, G. and S., and on one man, as control. The cholesterol determinations were done on these three volunteers for a period of two months, so that the behavior of the blood cholesterol could be studied during two monthly periods in each of the women. Both women were single, G. was twenty-three and S. thirty-three years of age; the man H. was married, thirty-six years old and the father of four healthy children. The women as well as the man were apparently in good health as they showed no clinical evidence of disease and were able to pursue their respective callings without interruption during the two months of the experiment. It was known, however, that S. had occasional attacks of gastric disturbance which usually occurred in spring and in autumn, suggesting the possibility of gastric or duodenal ulcer, but all clinical tests had failed to confirm this suspicion.

The cholesterol curves of the three volunteers showed fluctuations within the normal range such as are found in all serial determinations, but the curves of the women do not show any tendency to cyclic variations. The changes in the cholesterol values are wholly independent of the menstrual period; they differ in G. and S. and the curve of H., the man, shows as many fluctuations, within the same range and as irregular in character as the curves of the two women. The very irregularity in the fluctuations of the cholesterol values is evidence that technical errors are not responsible for these minor changes, because a parallelism in the behavior of tests made on a number of persons on the same day might lead one to suspect a common element of technical error such as impurity in one of the reagents, whereas slight differences in the values are to be expected in different persons, living under different conditions.

A common factor which, as will be discussed in Chapter XII, may have had some influence on the occurrence of somewhat subnormal split cholesterol values in several of the blood cholesterol determinations on G., S., and H., is the exposure of these three volunteers to carbon monoxid. Whereas G. lives in a house close to the railway tracks and therefore is exposed to great amounts of smoke from "switching" engines in addition to which the furnace in her house is known to be old, S. volunteered the information that she had "felt miserable" many a time when living in a house in which the furnace fumes were perceptible by the sense of smell; H. attended for several years to the heating of a furnace which was eventually discovered to be markedly defective, and his occupation as chauffeur naturally brings him into contact with exhaust gas, although he is fully aware of the dangers of automobile exhaust and very careful about avoiding it as much as possible.

In view of the findings in the blood of G., S., and H. the questionable effect of the menstrual period will not be taken into further consideration in the discussion of my observations on the behavior of the blood cholesterol under various conditions.

BIBLIOGRAPHY

1. Albrecht, H. and Hecht, V.: Ueber das Mauskarzinom. Wien. klin. Wchnschr., 1909, xxii, 1737-1742.

2. Allen: Quoted by Biedl.

3. Aschoff, L.: Quoted by Rothschild.

4. Aschoff, L.: Zur Cholesterinesterämie der Schwangeren. Wien. klin. Wchnschr., 1911, xxiv, 559.

5. Autenrieth, W. and Funk, A.: Ueber kolorimetrische Bestimmungsmethoden: Die Bestimmung des Gesamtcholesterins im Blut und in Organen. München. med. Wchnschr., 1913, lx, 1243-1248.

6. Bacmeister and Havers: Zur Physiologie und Pathologie des Cholesterinstoffwechsels. Deutsch. med. Wchnschr., 1914, xl, 385-388.

7. Bainbridge, W.S.: The influence of pregnancy on the development, progress, and recurrence of cancer. Am. Jour. Obst., 1918, lxxvii, 21-28.

8. Bashford, E.F., Murray, J.A. and Cramer, W.: Quoted by Woglom.

9. Biedl, A.: Innere Sekretion. Berlin, Urban u. Schwarzenberg, 1913, 2 auf.

10. Chauffard, A.: Variations de la cholestérinémie durant le cycle menstruel. Presse Méd., 1917, xxv, 329-330.

11. Döderlein, A.: Röntgenstrahlen und Mesothorium in der gynäkologischen Therapie, insbesondere auch bei Uteruskarzinom. Monatschr. f. Geburtsh. u. Gynäk., 1913, xxxviii, 559-593.

12. Falta, W.: Die Erkrankungen der Blutdrüsen. Berl., Springer, 1913, 562 pp.

13. Haaland, M.: Beobachtungen über natürliche Geschwulstresistenz bei Mäusen. Berl. klin. Wchnschr., 1907, xliv, 713-719.

14. Herzog, M.: On tumor transplantation and inoculation. Jour. Med. Res., 1902, viii, 74-82.

15. Hueck, W.: Die Bedeutung der Nebennieren für den Kohlenhydrat- und Cholesterinstoffwechsel und über die Beziehung des Cholesterins zum Fettstoffwechsel. Centralbl. f. allg. Path. u. path. Anat., 1914, xxv, 397.

16. Joslin, E.P.: The treatment of diabetes mellitus with observations upon the disease based upon thirteen hundred cases. Philadelphia, Lea, 1917, 559 pp.

17. Kendall, E.C.: The physiologic action of thyroxin. Endocrinology, 1919, iii, 159-163.

18. Kirk: Quoted by Biedl.

19. Lorand: Quoted by Wolff, iiib, 451.

20. Luden, G.: Studies on cholesterol. IV. Experiments concerning the relation of the diet, the blood cholesterol and the "lymphoid defence". Jour. Lab. and Clin. Med., 1917-1918, iii, 141-174.

V. The blood cholesterol in malignant disease and the effect of radium on the blood cholesterol. Jour. Lab. and Clin. Med., 1918-1919, iv, 849-864.

VI. The value of blood cholesterol determinations and their place in cancer research. Jour. Lab. and Clin. Med., 1918-1919, iv, 719-735.

21. McCallum, W.G.: A text-book of pathology. Philadelphia, Saunders, 1918, 801.

22. Morau, H.: Recherches experimentales sur la transmissibilite de certains neoplasmes (epitheliomas cylindriques). Arch. de med. exper. et d'anat. path., 1894, vi, 677-705.

23. Osborne, O.T.: Ovary: corpus luteum. New York Med. Jour., 1918, cviii, 401-405; 447-451.

24. Pusey, W.A.: Personal communication to Dr. J. H. Stokes.

25. Robertson, T.B. and Burnett, T.C.: The part played by the hydroxy-benzol radical in the acceleration of the growth of carcinomata by cholesterol and by tethelin. Jour. Cancer Res., 1918, iii, 75-91.

26. Rohdenburg, G.L.: Fluctuations in the growth energy of malignant tumors in man, with especial reference to spontaneous recession. Jour. Cancer Res., 1918, iii, 193-225.

27. Rothschild, M.A.: Zur Physiologie des Cholesterinstoffwechsels. V. Der Cholesteringehalt des Blutes und einiger Organe im Hungerzustand. Beitr. z. Path. Anat. u. z. allg. Path., 1915, lx, 227-231.

28. Schotten: Quoted by Biedl.

29. Slye, Maud: The relation of pregnancy and reproduction to tumor growth. Studies in the incidence and inheritability of spontaneous tumors in mice. Problems in the behavior of tumors. Tenth Report Jour. Cancer Res., 1920, v, [illegible].

30. Starr: Quoted by Biedl.

31. Uhlenhuth and Wiedans: Mitteilunger über einige experimentelle Krebsforschungen. Arb. a. d. k. Gsndhtsamte., 1909, xxx, 434-444.

32. Vincent, S.: Internal secretion and the ductless glands. London, Arnold, 1912, 484 pp.

33. Wacker, L.: Das Cholesterin und seine Begleitsubstanzen im menschlichen Depotfett beim Carcinom. Ztschr. f. physiol. Chem., 1912, lxxx, 389-408.

34. Woglom, W.H.: The study of experimental cancer. New York, Columbia Univ. Press, 1913, 288 pp.

35. Wood, F.C. and Prime, F.: Lethal dose of roentgen rays for cancer cells. Jour. Am. Med. Assn., 1920, lxxiv, 308-312.

Chapter X

CHOLESTEROL AND BACTERIAL GROWTH: WITH REFERENCE TO THE WORK OF MANFREDI

The cholesterol content of the blood seems to further the multiplication of body cells, by some as yet unexplained mechanism, but to hamper the multiplication of many varieties of pathogenic bacteria.

Brailsford Robertson has suggested that cholesterol acts as a catalyzing agent in the process of cell division. It seems equally possible, however, that cholesterol is used directly as material for the formation of cells. Doree, Gardner, Ellis and Lander have shown that the chick embryo unquestionably converts the cholesterol of the egg yolk into the cells of which the embryonic tissues are composed, the cholesterol of the yolk being gradually used up as the embryo increases in size. The latter observations suggest that in mammals (?) the cholesterol content of the blood may furnish an opportunity for cell multiplication, an opportunity proportional to the cholesterol concentration. Factors favoring the increase of the blood cholesterol would thus promote cytoplasia, while agents reducing the cholesterol concentration might be expected to impede cell division.

Sporadic observations concerning the increase of the blood cholesterol values at the onset of acute bacterial infections have been reported by various writers, but the technic used in their determinations has not been uniform; their findings, therefore, do not furnish conclusive evidence. In cholesterol tests technical details affect the results to no small degree. Serial determinations on a number of persons by means of a uniform standardized technical procedure, however, such as I have used since 1916, can be expected to furnish definite information with regard to the behavior of the blood cholesterol in acute or chronic bacterial infections.

The researches of Manfredi on the effect of cholesterol on bacterial growth in vitro and my observations on the blood cholesterol in bacterial infection point to some connection between the blood cholesterol values and the problems of immunity. A brief outline of Manfredi's work is given here, first, because of its bearing on cancer research, and, second, as a tribute to an investigator, whose work is little known, although its thoroughness deserves emulation and its significance may prove far reaching.

The data for my outline of Manfredi's work were taken from the original, which I secured in order to know all the details of the technic; but it is impossible to do justice in a short summary to all the valuable information contained in the original article.

Manfredi comes to the conclusion that "cholesterol apparently has a protective part to play in the organism" by means of the following series of experiments. Parallel cultures of sixteen types of pathogenic bacteria were made repeatedly in three different mediums: (1) plain liquefied agar-agar, (2) agar to which sterile olive oil had been added, the mixture being shaken a considerable length of time and then rapidly cooled on ice to secure a homogeneous emulsion, and (3) agar with the addition of olive oil in which small quantities of cholesterol had been dissolved, the same precautions being taken to make the mixture absolutely homogeneous. Olive oil was used as a solvent for the cholesterol because it did not appear to influence the growth of the cultures. The same stock supply of agar, oil and cholesterol was employed throughout the experiments. The proportion of agar and oil was kept constant, but the cholesterol concentration was gradually increased from 0.5, 1.0, 2.0, 5.0, and 10.0 to 1000 parts of the medium. In every instance the organisms for the three parallel cultures were taken from the same stock culture. The organisms used were typhoid bacilli (laboratory culture, and cultures from two patients in the second stage of the disease); paratyphoid A (laboratory culture) and paratyphoid B (from two patients at different stages);

Bacterium coli (laboratory culture, and a recent laboratory culture); Staphylococcus aureus (recent culture from an abscess); Bacillus prodigiosus; Bacillus chromogenus; two different cultures of streptococci in erysipelas, two strains of streptococci in puerperal fever; one strain of diphtheria and two strains of cholera bacilli. All these organisms grew luxuriant, and produced large cultures both in the plain agar and in the agar mixed with oil alone; the addition of cholesterol to the medium, however, checked their growth in proportion to its concentration and to their idiosyncrasies. Bacillus prodigiosus for instance, seemed to thrive on cholesterol; a concentration of 10:1000, which inhibited the growth of all the other microorganisms produced cultures that were larger and denser than those in the control mediums. The effect of cholesterol on the other bacilli is tabulated by Manfredi as follows:

Organisms	Effect of cholesterol Concentrations		
B. prodigiosus	Promotion	5:1000	Inhibition by greater concentration
B. typhosus	Promotion	2:1000	Inhibition by greater concentration
S. aureus	Promotion	2:1000	Inhibition by greater concentration
B. chromogenes	Promotion	2:1000	Inhibition by greater concentration
S. erysipelatis	Indifference to less than	1:1000	Inhibition by greater concentration
S. puerperalis	Indifference to less than	1:1000	Inhibition by greater concentration
B. diphtheriae	Indifference to less than	1:1000	Inhibition by greater concentration
B. cholerae	Indifference to less than	1:1000	Inhibition by greater concentration
Bacterium coli	Slight inhibition by	1:1000	Inhibition by greater concentration
B. paratyphosus A and B	Slight inhibition by	1:1000	Inhibition by greater concentration

In some instances two strains of the same organism showed different degrees of susceptibility to inhibition by cholesterol; thus, one strain of cholera bacilli still gave "good" cultures in a concentration of 2:1000, while the other only produced "fair" or "medium" cultures. The same was found to apply to the streptococcus of erysipelas.

I have shown that in normal human blood the Bloor I cholesterol values range from 70 to 100 mg. per 100 c.c., representing a cholesterol concentration of 0.07 to 0.1 per cent or of 7 to 10 in 10,000. The majority of the patho-genic bacteria studied by Manfredi were, therefore, indifferent to a cholesterol concentration of 1:1000 (or 10:10,000), that is, to the average concentration of normal human blood, but their growth was impeded by concentration from 10 to 20: 10,000, with the exception of the Bacillus prodigiosus, the Bacillus typhosus, Staphylococcus aureus and Bacillus chromogenus.

Manfredi's observations recall certain other bacteriologic findings and clinical data for both of which they seem to offer an explanation: (1) The typhoid bacillus can be grown on undiluted human blood and bile, but other pathogenic bacteria refuse to grow on blood agar containing more than one third human blood to two thirds of agar.* Influenza bacilli were found by McKribben** of Johns Hopkins to grow satisfactorily, however, on the undiluted blood of rabbits; Figures 2 and 3 show that the blood of rabbits has a cholesterol concentration of only 4 to 6 per 10,000, that is, a concentration equal to a 1:3 dilution of normal human blood. (2) The benefit of Coley's treatment in malignant conditions seems explicable by the manifest avidity of Bacillus prodigiosus for cholesterol, which would tend to decrease the amount of cholesterol available for cell multiplication; the curative effects of erysipelas on malignant growths is well known and it will be remembered that Coley uses both Bacillus erysipelas and Bacillus prodigiosus in his treatment. (3) Many observers have commented on the relative immunity to bacterial infection observed in patients suffering from carcinoma; the blood of the majority has been shown to contain high cholesterol concentrations. On the other hand patients suffering from myxedema, whose blood cholesterol values are far above normal, are prone to succumb to bacterial infection, a clinical observa-

* Personal communication by Dr. B. F. Sturdivant, Assistant in Experimental Bacteriology, Mayo Foundation.

** Observations on the growth of influenza cultures by Dr. McKribben of Johns Hopkins, personal communication to Dr. J. W. Crane, written to me by Dr. Crane.

tion that seems hard to explain in the light of Manfredi's findings. (4) After the influenza epidemics, however, a marked tendency to neoplastic recurrences has been noticed in a great number of cases. This fact suggests that the increase of the blood cholesterol, which was intended to combat the growth of the invading bacteria, being either inadequately utilized or inadequately eliminated, remained available for the promotion of cell division.

If, as Manfredi's experiments suggest, the cholesterol concentration in the culture medium determines the rate of growth of bacteria, a rise of the blood cholesterol values at the onset of bacterial infections would represent a defensive reaction, and a measure intended to increase the resistance to bacterial invasion might, logically, be expected to produce a rise of the Bloor I blood cholesterol values. My observations on the cholesterol content of my blood and on that of four friends during the various waves of influenza between 1918 and 1920 support these deductions. In the diagrams presenting a graphic record of my findings the letter A represents my blood, while B, C, D and F indicate the blood of the other four persons, respectively on whom serial observations could be made; the Roman figures with these letters refer to various charts belonging to one person.

At the beginning of the epidemic of influenza in the autumn of 1918 (the patient on whose blood I have made weekly observation since 1917) A and B were given three weekly injections of Dr. Rosenow's prophylactic vaccine. This vaccine (No. 409) contained pneumococci (Types I, II, and III) green-producing hemolytic streptococci, staphylococci, and a small percentage of influenza bacilli. Six days after the third injection (Oct. 29, 1918) the Bloor I cholesterol of A (Fig. 26) rose to 163 mg. A higher concentration than it had ever reached before. (Fig. 18, compare with Figures 35 and 42 and the key to the diagrams of blood constituents, Fig. 22). A similar, though less marked rise followed a fourth injection of vaccine (No. 455) Nov. 19, 1918, which contained no influenza bacilli (Fig. 26). January 2, 1919 my Bloor I values had dropped to 83 mg. (Fig. 26).

Not long afterward I began to develop a few symptoms, sore throat, sore chest, severe headache, that suggested the onset of influenza: I had been entirely free from the disease when the epidemic was at its height and had come into contact with many patients. A blood test, Jan. 17, 1919, showed that my cholesterol had again risen to 195 mg., and the symptoms disappeared without medication, although I took no special precautions and continued to work as usual. In the hope of obtaining more evidence concerning the effect of the vaccine on the blood cholesterol values, I had a fifth injection Jan. 23, 1919. This injection did not cause a rise in the blood cholesterol, but it was followed by a severe local reaction, resulting in the formation of a small cyst-like nodule. The little nodule gave no trouble, and remained unchanged for more than three months, I had it excised April 11, 1919, because it was beginning to decrease in size, and I wished to examine it microscopically before it disappeared. To my regret it proved to be merely a small cyst lined with endothelium (Fig. 26a). I was unable to make a determination of the contents since the liquid escaped during the excision. I expected a cholesterol deposit, similar to the one which I had obtained in one of my cholesterol-fed goats; the cyst on the animal's nose had shown a cholesterol concentration ten times higher than its blood at the same time. The sixth injection of vaccine (No. 455) March 21, 1919, shortly after my return from a five weeks' vacation failed to show any rise of the blood cholesterol values (Fig. 26); but I did not contract the disease, although I was looking after an influenza patient at the time, and even though a culture of Pfeiffer bacilli was obtained from my naso-pharynx, April 6, 1919, by Dr. Anna Hatfield.

In the case of B the blood cholesterol seems to have responded by a rise similar to that observed in my blood. But the rise was more gradual and reached its maximum, 173 mg., on the fourteenth day after the second dose of vaccine. A second rise to 163 mg. was found on the twenty-sixth day after the third injection. Although B also came into contact with patients suffering from influenza, she did not contract the disease during the epidemics of 1918 and 1919 (Fig. 35, compare with Figs. 26 and 45). In consideration of B's operation for carcinoma of the breast in 1917 4 mg. of thyroxin were given shortly after the second injection, as I feared that a continuence of the high blood cholesterol values might promote neoplastic proliferation. Figures 34, 35, 36, and 37 show the drop of the Bloor I values following the administration of the thyroid hormone and the subsequent rise produced by the third dose of vaccine.

Further evidence of the increase of the blood cholesterol during exposure to bacterial infections is offered by the blood cholesterol values of A, B, C, and D in August, 1919. (Figs. 26, 35, 38, and 41). An epidemic of "influenza-like colds" prevailed in Rochester during the entire month of August: B had one of these severe colds; D volunteered the information that he "felt as if he was getting influenza" when his blood was taken for the determination of August 21. A sharp rise in the blood cholesterol was found in this determination and a similar marked increase could be observed in the blood of A, B, and C, although the increase did not occur on the same date in every instance. It seems reasonable in view of the prevailing epidemic to interpret these sudden changes in the chemical composition of the blood as a defensive reaction against bacterial invasion.

During the epidemic of influenza in January and February, 1920 the effect of the prophylactic vaccine on the blood cholesterol values was less marked than in my previous observations, possibly because another type of vaccine (No. 500) was used. The symptoms presented by the disease at this time also differed somewhat from those seen in the epidemics of 1918 and 1919. In a great many cases, besides those in which cholesterol determinations were made, the main features of the infection seemed to be the formation of numerous small ulcers in the nose and naso-pharynx, intense headache, acute or subacute conjunctivitis, and a more or less marked rise of temperature. I was able to study the relation between the onset of bacterial infection and the changes in the cholesterol values by serial determinations on the blood of F and D, who contracted the disease, and of A and C who remained immune.

In the case of F, an unmarried woman, aged thirty-two years, soreness and ulceration of the throat were first noticed Jan. 8, 1920. During the two following days the Bloor I values were found to be unusually high, 204 and 201 mg. (Fig. 42). There was no febrile reaction at that time. After the cholesterol content of the blood had been determined, January 10, the patient was given an injection of vaccine No. 500. January 11 the temperature rose to 103°F; evening temperatures ranging from 101.8° to 102°F persisted until January 21. Six days after injection of the vaccine a cholesterol determination made at 9 a.m., when the temperature was practically normal, showed that the Bloor I values had dropped to 80 mg. This observation seemed to confirm the lowering effect of febrile reactions on the blood cholesterol values. It is possible, however, in the light of Manfredi's investigations, that the great reduction of the Bloor I cholesterol prevented the complete elimination of the invading organisms. The patient certainly did not clear up the infection thoroughly. During the weeks following she continued to suffer from recurrent, minor attacks of ulcerative pharyngitis, and finally it appeared that the organisms which produced the ulcers in the throat invaded the pleura. February 10 F began to experience a sharp pain in her left side on profound expiration. The short characteristic cough, which accompanied pleural involvement developed a few days later. The pain was restricted to a relatively small area, but the area seemed to shift. These symptoms suggested that small ulcers might be forming on the pleura similar to those that had been seen in the throat. Pleural friction could only be heard very faintly during one day; no evidence of pleural effusion was found at any time, and minute pleural abscesses cannot be demonstrated by clinical methods. The clinical picture, however, recalled the syndrome described by Kelly and Weiss under the name of "diaphragmatic pleurisy"; even the "characteristic" tenderness along the edge of the trapesius, to which these writers have called attention, was present. It is interesting in this connection that at necropsies during the epidemic of influenza in the earlier part of 1920, "small and minute abscesses in or immediately beneath the pleura" were found by Symmers and Dinnerstein; their observations had not yet been published when the symptoms of F suggested this type of pleural involvement.

The changes in the cholesterol content of F's blood during this exacerbation of the infection are interesting. Her Bloor I values had not been high, 120 mg., before February 10; they showed a sharp rise February 14 to 180 mg. As a prophylactic measure, in order to prevent, if possible, the development of pneumonia, a second dose of vaccine (No. 500) was given February 15 at 6 p.m. The evening temperature, which had been 100°F before injection of the vaccine, did not exceed 99°F on the following day, but continued to reach 100°F until February 20. Five days after injection of the vaccine February 20 the Bloor I values had again dropped to 120 mg. It would seem as if the reduction of the blood cholesterol again hampered the complete elimination of the infection: severe neuritis in both arms developed February 21, but all the symptoms had cleared up about March 5, when the Bloor I values were found to have risen to 180 mg. Roentgenographic examination of the chest, March 8, failed to reveal the slightest pathologic change in the lungs or the pleura.

Although the foregoing findings undoubtedly point to the relation between the process of immunization and the blood cholesterol values, many factors must be taken into account in the case of F. Her clinical history, which cannot be discussed in detail on account of its length, contains many data suggestive of adrenal insufficiency. She had suffered from chronic appendicitis for twenty years; the appendix had ruptured, but walled itself off at the age of seven; appendectomy at the age of twenty-seven revealed the extensive adhesions which had prevented general peritonitis. She had had two other major operations and numerous attacks of influenza previous to the one that has been discussed, and she had been exposed to chronic carbon monoxid poisoning for several months during the autumn of 1919. Chronic bacterial infections are known to tax the efficiency of the suprarenal glands. The depressing effect of carbon monoxid on the adrenal will be discussed in Chapter XI. It seems probable, therefore, that adrenal insufficiency may be responsible for the half-hearted way in which F fought the infection. Since it is admitted that the adrenals play an important part in the process of immunization (Sajous, Da Costa), that their activity is markedly impaired by influenza (Cowie and Beaven), and they must undoubtedly be considered "one of the chief regulators of cholesterol metabolism" (Study I). In the main my observations on the blood cholesterol values of F seem to be in accordance with those that I have previously reported: the onset of bacterial infection and subsequent exacerbations were accompanied by a sharp rise, while febrile reactions representing an acceleration of the metabolic rate were followed by a marked reduction of the blood cholesterol values.

In the case of D, a married man, aged thirty-two years, the influence of bacterial infection on the blood cholesterol was even more striking and the findings seemed less hard to interpret. A prophylactic injection of vaccine (No. 455) was given Jan. 15, 1920, when D was in good health. The blood cholesterol values were practically normal at the time and the vaccine does not appear to have affected them to any marked extent (Figs. 40 and 41). The Bloor I values did not exceed 120 mg., representing a cholesterol concentration of 12 to 10,000, that is, practically the concentration which Manfredi had found insufficient to retard the growth of the majority of pathogenic bacteria. The first symptoms of the epidemic, severe headache and nausea, were experienced by D January 25. The symptoms subsided in a few days and their severity was not sufficiently great to keep the patient at home. It seems as if the lack of marked increase in the blood cholesterol values prevented the thorough elimination of the infection for D to the same extent that it did for F, for D also had a second and more severe recurrence of influenza. February 20 he developed symptoms of sinusitis, with intense headache, marked injection of the conjunctiva and severe pain in the eye-balls, which obliged him to stay in bed several days. The symptoms were clearing up February 26 when the Bloor I cholesterol values were found to have risen to 164 mg.

My blood cholesterol showed a marked increase, 170 mg. February 14, and again I remained immune as during the previous epidemics, although I was nursing F and visiting D almost daily during his illness (Fig. 30).

The inhibiting effect of cholesterol on bacterial growth is not so clearly shown in the case of C, aged thirty-four years, wife of D. Her Bloor I values ranged from 120 to 140 mg. during the epidemic and did not show any marked increase, yet she remained immune although she took care of her husband during his two attacks of influenza and although the baby, whose history has been given in Chapter IX, lived at her home and also showed symptoms of the prevalent infection. Whether these findings indicate that other blood constituents furnished the elements necessary to immunity is a matter of conjecture at present. The hemoglobin content of C's blood had been persistently high (00 per cent) for more than two years (Figs. 37, 38 and 39); other determinations which I had made at intervals since 1914, and which are not recorded in the diagrams, had shown that this high level had been constant for nearly six years. The correct interpretation of C's cholesterol curve is, moreover, rendered difficult by the possible effect on the chemical composition of the blood of two antagonistic factors: slight carbon monoxid poisoning and organotherapy. Previous observations on my blood had shown that exposure to carbon monoxid tends to reduce the Bloor I values, while the ingestion of dessicated adrenal (Amour's Dessicated Suprarenal Gland, U.S.P.) seems to increase the Bloor I cholesterol. During the epidemic of influenza C had been repeatedly exposed to small amounts of carbon monoxid by the accidental closing of a damper in her furnace. It was only discovered several weeks later that the damper "closed itself" through the vibration caused by passing vehicles. Although these facts were unknown to me at the time I had given C small doses of dessicated adrenal whenever her symptoms recalled the effects of the poisonous gas, which I had learned to recognize by my own experience and for which this form of organotherapy had proved beneficial. It is therefore impossible to decide at present whether C's immunity to influenza was connected with the cholesterol and the hemoglobin content of her blood, or produced by the administration of dessicated adrenal, or merely the result of other unknown factors.

Cholesterol and postoperative suppuration. It is a well-known fact, that postoperative suppuration occurs for no demonstrable reason in some patients, while the wounds of others heal by first intention although identical precautions were used. It is not impossible that low blood cholesterol values furthered the multiplication of the pathogenic bacteria in the first instance, and that high blood cholesterol values checked bacterial growth in the second. Although I have not yet had the opportunity to verify this assumption by systematic investigation many chance observations seem to support it; B, for example (Figs. 33, 34, 35, and 36) had high blood cholesterol values even after a Halsted operation for carcinoma of the breast (all operative procedures tend to lower the blood cholesterol), and in her case healing was rapid and by first intention.

The advantages of combating postoperative suppuration by means of cholesterol need no comment, but the administration of cholesterol to this end presents many problems. The usual cholesterol solvents, ether, alcohol, chloroform, and benzin are little suited for intravenous injections; the evaporation of the solvent, not to mention its irritating properties, might result in the precipitation of cholesterol crystals, and the latter might act as a foreign body or even produce embolisms. Olive oil would constitute an ideal, nonirritating solvent, but the necessary process of sterilizing it before injection is likely to cause a disintegration of the cholesterol molecule, although no definite data could be found bearing on this part of the problem. It was my intention to test the immunising effect of cholesterol by animal experiments. Rabbits had been selected for the purpose, but those available at the time were small and the ear-veins (used by Rothschild in his experiments) failed to give a sufficient amount of blood for determinations by the Bloor methods, while the animals did not survive repeated bleeding from the heart. The blood of rabbits, moreover, has a most provoking rapidity of coagulation not usually found in human blood. Clotting of the blood mars the accuracy of the determination and the use of citrates (sodium or potassium) affects the cholesterol values. Animals as well as human beings seem to possess individual cholesterol levels, that is, the cholesterol content of the blood of one animal will be, normally, higher than that of another; consequently a series of determinations are needed to establish the cholesterol level of a given animal. Most of the rabbits died before their level had been ascertained and the effects of chronic carbon monoxid poisoning, which will be discussed in Chapter XI, prevented my concluding this experiment by incapacitating me for work during two months.

The use of cholesterol for the purpose of increasing immunity has been advocated by Barbary, who obtained satisfactory results with it in the treatment of sick and wounded at Nice during the war (1916). But Barbary did not use cholesterol alone; the injections which he gave consisted of 0.2 gm. cholesterol, 0.3 gm. camphor, and 0.0005 gm. strychnin dissolved in olive oil, which had been "washed" in alcohol.

Although the results obtained by Barbary (only five of 754 patients developed septic complications) are by no means questions, they do not show clearly what part the cholesterol played in the process of immunisation, first because he did not make any blood cholesterol determinations, and second because he added strychnin and camphor to the injections. According to Sajous, strychnin stimulated the "adrenal system", and evidence is accumulating that the adrenal plays an important part in immunity. The effect of camphor on the adrenal and on the chemical composition of the blood has not been studied, as far as I can ascertain; the therapeutic value of camphor is admitted by some and denied by others. Cushny classes camphor "with the picrotoxin-group of convulsive poisons, which resemble each other closely in action, but of whose chemistry little is known beyond the fact that they do not contain nitrogen". Bastedo condemns the use of camphor altogether; he says: "Any good effects upon the circulation are extremely problematic, the ones reported being a mild stimulation of the heart muscle, and mild stimulation of the vagus and the vasoconstrictor centers . . . . There is some stimulation of the respiratory center after large doses" and he adds that, as a heart stimulant, "it is entirely unreliable". My own experiences with repeated injections of camphor, both after operations and in chronic carbon monoxid poisoning, do not corroborate this verdict, but suggest that camphor exerts a marked influence on the adrenals. The testimony of those at the front who used camphor makes it seem likely that the therapeutic value of camphor will shortly be as much appreciated in America as it long has been in Europe. The control of bacterial infection, reported by Barbary, may, therefore, be largely the result of the stimulation of the suprarenal glands by strychnin and possibly by camphor; but his results do not furnish conclusive evidence that the cholesterol which he injected was utilized for the reduction of bacterial growth. The work of Manfredi, on the other hand, the behavior of the blood cholesterol during the epidemics of influenza in Rochester, and the evidence, which we possess, that the adrenal is intimately connected with the body's defensive measures against bacterial invasion (Sergent, Harrower, Sajous, Cowie and Cramer) and with cholesterol metabolism (Rothschild, Landau, Stewart, Hueck, McMeans, Luden and others) strongly suggests that cholesterol is an important factor in immunity. The recent work of Mareto and Villanueva confirms this assumption.*

* In recent publication, which had not appeared when the above was written, Barker corroborates the writer's observations by the following statement: "Under the influence of infection, the suprarenals become red and turgid, they increase in weight, and from the beginning of the infection, the cortex pours out its reserve of cholesterol into the blood stream and proceeds to secrete more".

The advantages to be derived from a better understanding of the exact part which cholesterol plays in the process of immunisation can hardly be overrated since the practical application of such knowledge would prove of value in nearly every branch of medicine, including surgery, obstetrics, internal medicine and epidemiology and embracing prophylaxis and therapeutics. Further investigations concerning the blood cholesterol values in bacterial infection and the effect of cholesterol on the growth of bacteria in vitro must therefore be looked on as of vital importance.

BIBLIOGRAPHY

1. Barbary, F.: Mise en état de défense de l'organisme infecté; méthode nouvelle; actions antihémolytique et antitoxique; applications pratique aux grands blessés de guerre. Bull. Acad. de méd., 1916, 3.s., lxxvi, 221-223. Abstr. Jour. Am. Med. Assn., 1916, lxvii, 1477.

2. Barker, L.F.: Diseases of the suprarenal glands. Nelson Loose-Leaf living medicine. New York, Thomas Nelson and Sons, 1920, iii, 230.

3. Bastedo, W.A.: Materia medica; pharmacology; therapeutics. Philadelphia, Saunders, 1915, 602 pp.

4. Coley, W.D.: Sarcoma of the omentum. Discussion. Ann. Surg., 1910, lii, 410.

5. Cowie, D.M.: The action of adrenalin on the leucocytes and erythrocytes. Contributions to medical and biologic research, dedicated to Sir William Osler, in honor of his seventieth birthday. New York, Hoeber, 1919, ii, 829-844.

6. Cowie, D.M. and Beaven, P.W.: On the clinical evidence of involvement of the suprarenal glands in influenza and influenzal pneumonia. Arch. Int. Med., 1919, xxiv, 78-88.

7. Cramer, W.: Observations on the functional activity of the suprarenal gland in health and in disease. Sixth Scientific Report of the Imperial Cancer Research Fund. London, Taylor and Francis, 1919, 1-21.

8. Cushny, A.R.: A text-book of pharmacology and therapeutics, or the action of drugs in health and disease. 6 ed. Philadelphia, Lea and Febiger, 1915, 702 pp.

9. Da Costa, J.C.: A handbook of medical treatment. Philadelphia, F.A.Davis Co., 1919, ii, 67-197.

10. Doree, C. and Gardner, J.A.: The origin and destiny of cholesterol in the animal organism. Part I. Proc. Roy. Soc. Lond., 1908, s.B., lxxx, 212-239.

Part III. The absorption of cholesterol from the food and its appearance in the blood. Proc. Roy. Soc. Lond., 1909, s.B., lxxxi, 109-128.

Part IV. The cholesterol contents of eggs and chicks. Proc. Roy. Soc. Lond., 1908, s.B., lxxxi, 129-132.

11. Ellis, G.W. and Gardner, J.A.: The origin and destiny of cholesterol in the animal organism. Part VI. The excretion of cholesterol by the cat. Proc. Roy. Soc. Lond., 1909, s.B., lxxxi, 505-515.

Part VIII. On the cholesterol content of the liver of rabbits under various diets and during inanition. Proc. Roy. Soc. Lond., 1911-1912, s.B., lxxxiv, 461-470.

Part IX. On the cholesterol content of the tissues, other than liver, of rabbits under various diets and during inanition. Proc. Roy. Soc. Lond., 1912, s.B., lxxxv, 385-393.

Part X. On the excretion of cholesterol by man, when fed various diets. Proc. Roy. Soc. Lond., 1913, s.B., lxxxvi, 13-18.

12. Gardner, J.A. and Lander, P.E.: The origin and destiny of cholesterol in the animal organism. Part XI. The cholesterol content of growing chickens under different diets. Proc. Roy. Soc. Lond., 1913-1914, s.B., lxxxvii, 229-236.

13. Harrower, H.R.: Practical hormone therapy; a manual of organotherapy for general practitioners. New York, Am. Pub. Co., 1916, 488 pp.

14. Hueck, W.: Die Bedeutung der Nebennieren für den Kohlenhydrat- und Cholesterinstoffwechsel und über die Beziehung des Cholesterins zum Fettstoffwechsel. Centralbl. f. allg. Path. u. path. Anat., 1914, xxv, 397.

15. Kelly, T.H. and Weiss, H.B.: The diagnosis and treatment of diaphragmatic pleurisy. With report of cases. Am. Jour. Med. Sc., 1918, clvi, 808-817.

16. Landau, M. and McNee, J.W.: Zur Physiologie des Cholesterinstoffwechsels. Beitr. z. path. Anat. u. z. allg. Path., 1914, lviii, 667-699.

17. Luden, G.: Studies on cholesterol. I. Observations on cholesterol retention as a factor in cell-proliferation. Jour. Lab. and Clin. Med., 1915-1916, i, 662-676.

II. Observations on the changes in the cholesterol content of the blood of goats, following cholesterol feeding alone, roentgen treatment alone, and cholesterol feeding combined with roentgen treatment and subsequent castration. Jour. Lab. and Clin. Med., 1916, xxvii, 273-297.

III. The influence of bile derivatives in Bloor's cholesterol determination (Preliminary report). Jour. Biol. Chem., 1917, xxix, 469-476; also Jour. Lab. and Clin. Med., 1917-1918, iii, 99-109.

IV. Experiments concerning the relation of the diet, the blood cholesterol and the "lymphoid defence". Jour. Lab. and Clin. Med., 1917-1918, iii, 141-174.

V. The blood cholesterol in malignant disease and the effect of radium on the blood cholesterol. Jour. Lab. and Clin. Med., 1918-1919, iv, 849-964.

VI. The value of blood cholesterol determinations and their place in cancer research. Jour. Lab. and Clin. Med., 1918-1919, iv, 719-735.

18. McMeans, J.W.: Tissue reactions in experimental hypercholesterinemia. Jour. Med. Res., 1916, xxxiii, 481-491.

19. Manfredi, L.: Sviluppo di alcuni germi in mezzi culturali addizionati di colesterina. Riforma med., 1917, xxxiii, 849-853. Abstr. Jour. Am. Med. Assn., 1917, lxix, 1479.

20. Morató, T. and Villanueva, G.: [Cholesterol as a factor in immunity and in production of agglutinins.] Med. Ibera, 1919, ix, 137. Abstr. Jour. Am. Med. Assn., 1920, lxxiv, 362.

21. Robertson, T.B. and Burnett, T.C.: The part played by the hydroxybenzol radical in the acceleration of the growth of carcinomata by cholesterol and by tethelin. Jour. Cancer Res., 1918, iii, 75-91.

22. Rothschild, M.A.: Zur Physiologie des Cholesterinstoffwechsels. III. Die Beziehungen der Nebenniere zum Cholesterinstoffwechsel. Beitr. z. path. Anat. u. z. allg. Path., 1915, lx, 39-65.

23. Sajous, C.E.: Internal secretions and principles of medicine. Philadelphia, F.A.Davis Co., 1919.

24. Sergent, E.: Quoted by Harrower.

25. Stewart: Quoted by McMeans.

26. Symmers, D., Dinnerstein, M. and Frost, A.D.: Differences in pathology of pandemic and recurrent forms of so-called influenza. Jour. Am. Med. Assn., 1920, lxxiv, 646-650.

Chapter XI

THE COMBUSTION PRODUCTS OF FUEL AND THE INCIDENCE OF CANCER.

THE MORTALITY AND MORBIDITY FROM CANCER IN ROCHESTER, MINNESOTA, 1907-1921.

It has long been known that the incidence of carcinoma is higher among chimney sweeps, than among any other class of men. Pott (1714-88) the great surgeon of St. Bartholomew's Hospital in London called attention to this fact as early as 1775.*

It has been generally accepted that the soot, with which the chimney sweep came into close, daily contact, when chimneys were still swept by boys climbing up inside the smoke stack, was chiefly responsible for the development of this particular type of malignancy, called "chimney sweeps' cancer". The experimental production of coal tar cancers in animals lends support to this conception, because soot and tar contain chemically allied substances.

Recent investigations have proved, however, that the combustion products of fuel, such as soot and smoke, are invariably associated with carbon monoxid, which, although strictly speaking a nontoxic gas, causes death in a few minutes when inhaled in concentrations of 0.2 or 0.3 of 1 per cent and produces severe, and often lasting metabolic disturbances in far lower concentration, because it displaces oxygen from its combination with hemoglobin. The red blood corpuscles are not destroyed in the process, as used to be assumed, but the oxygen deficit which results is responsible for the fatal effects as well as for the transient symptoms. Harris (1919), the director of the Bureau of Preventable Diseases in the Department of Health of New York, proved that very severe symptoms of carbon monoxid poisoning were caused suddenly by the smoke of a neighboring chimney in seventy-three of 125 men employed in a clothes manufacturing establishment,

* A fall in the street caused Pott to sustain the fracture of the fibula which bears his name and his epoch-making pamphlet on caries of the spinal vertebra (Pott's disease) was the indirect result of this injury, which confined him to his bed for a long time and made him take up authorship.

when the wind forced the smoke into the workrooms because a door, which closed a staircase to the roof, had been left open.

The correlation of knowledge should be the primary object of scientific investigation; a fact, to which Hoffman emphatically called attention at the meeting of the American Association for the Advancement of Science (Toronto, 1922). When the influence of the combustion products of fuel on the incidence of cancer is the object of research, and the influence of metabolic disturbances on the development of malignancy the subject of discussion, established data concerning coal-tar cancers as well as carbon-monoxid poisoning should therefore be borne in mind.

Bierich is the first investigator who paid attention to the metabolic disturbances which accompany the production of tar cancers in animals; he observed that his mice "ate a good deal of the tar in their endeavors to remove it" and that they developed renal symptoms, controlled by chemical analysis, within a few days after the first application of tar; his work has been described in detail (Chapter V, 149). Many therapeutic measures are based on the reabsorption of medicaments applied to the skin; the mercury inunctions in syphilis for example. The deduction that reabsorption of the tar may play a part in the production of tar cancer does not seem altogether without foundation. Nor does it seem improbable that three factors combined are responsible for the development of the chimney-sweep cancer, namely, (1) local irritation reducing the normal resistance of the cells in the affected area, (2) the metabolic disturbances produced by the reabsorption of soot through the skin, and (3) the deleterious effects on the body as a whole of chronic carbon monoxid poisoning. During his daily excursions in smoke stacks the chimney sweep is likely to have inhaled a considerable amount of stale smoke, which failed to rise when the flues were allowed to cool for cleaning; the down-draught produced in cold chimneys, which sends the smoke back into the rooms when the chimneys are used for the first time in autumn, is a phenomenon which few people can have failed to observe, and the persistency with which smoke "hangs around" in a locality, unless propelled by strong draughts, is equally well known. The symptoms of chronic carbon monoxid poisoning are numerous and diverse, as a rule apparently insignificant; their onset is insidious; the condition is "either overlooked or misinterpreted in nine cases out of ten" (Luden, 1921); "there are probably many more cases of the chronic form (of intoxication) than are usually recognised" (Sayers, 1922).

The effects of carbon monoxid on the organism have been made the object of extensive investigations by the U.S.Bureau of Mines in connection with a tunnel for automobile traffic under the Hudson river. (Henderson, Haggard, Prince and Wunderlich, Teague, Sayers and others). It was proved that the exhaust gas of automobiles using gasoline contains no less than from 4 to 12 per cent of carbon monoxid and that the exhaust of trucks in which the so-called "benzol mixture" is used contains an additional percentage of highly toxic compounds. Experiments on animals as well as the heroic tests made by Henderson and his collaborators on themselves showed, moreover, that the time of exposure multiplied by the concentration of carbon monoxid gives a quotient, which furnishes an approximate idea of the severity of the symptoms that are to be expected. The concentration of carbon monoxid is expressed in terms of a given number of parts of the gas in 10,000 parts of air. Thus, six parts of carbon monoxid (6:10,000) inhaled for one hour will produce symptoms lasting from one to several days according to the physical condition of the victim; somewhat higher concentrations (9:10,000 to 15:10,000) may produce rapid loss of consciousness. The usual symptoms are headache, nausea, lassitude, weakness in the legs and cardiac irregularities. The inhalation of low concentrations of the odorless and colorless, but deadly gas for prolonged periods is known to have a markedly deleterious influence on general health. I had the rare opportunity of studying the syndrome of chronic carbon monoxid during a period of nine weeks in three friends and myself before the cause of the symptoms (a defective furnace) had been discovered: a careful record had been kept of the symptoms, as the result of scientific curiosity as certain of the symptoms baffled interpretation, while others, which seemed explicable at first, presented conflicting evidence. A detailed account of this experience has been published in which attention is called to the ubiquity of carbon monoxid in modern civilised life, to the striking resemblance of many symptoms of chronic carbon monoxid poisoning to the established and acknowledged manifestations of certain types of endocrine dysfunction and to the relation of this type of chronic intoxication to many social, economic and domestic problems; an extensive bibliography is also given. Wilmer(1921) refers to carbon monoxid as "the Frankenstein of modern civilisation" in an article dealing with injuries to the eye resulting from carbon monoxid poisoning: he gives description of a "haunted house" in which the ghosts proved to be the visual and auditory hallucinations which the inhabitants experienced under the influence of the fumes of their furnace.

The delicacy of the chemical reactions within the organism and the incredibly small quantities in which chemical substances are capable of creating havoc in the body are facts, not generally realised, much less visualised. Yet, knowledge only becomes our mental property after it has been visualised, that is, transformed into a series of vivid mental pictures with the aid of the imagination.

The numerous investigations of Stewart and Rogoff (1918-1920) have proved conclusively that adrenalin is physiologically active in a concentration of one part in 330 millions: I pointed out (1921) that such a concentration may be obtained by diluting a small glass of whiskey (10 c.c.) with the combined content of 1320 city sprinkling carts, that is 826,000 gallons of water, and that the procession of sprinkling carts would be little less than six miles long.

Hamilton (1921), in her admirable survey of industrial diseases, has shown that minute amounts of lead and arsenic produce severe clinical symptoms. She calls attention in a recent publication (1922) to the growing menace of benzene (benzol) poison in Americanindustries, and she shows that coal tar distillates are being used more and more extensively in the rubber trade, in the shoe trade, in the making of straw hats, as a solvent for fabrikoid,* in sealing mixtures for tin cans and as a substitute for gasoline in motor-car fuel. The toxicity of benzol compounds is illustrated by an incident, related by Hamilton in connection with many other similar occurrences: "Even greater precautions had been taken in an English tank car which had been emptied of benzene, washed with water, then steamed out, then left for twenty-four hours full of water, washed out twice, boiled for twelve hours, and finally left for ten days with the 16-inch (40 cm.) manhole open. Nevertheless, the man who was sent in collapsed, and though he was pulled out in time, one of his rescuers died."

If animal tissues respond to a constantly supplied and constantly used "home product" like epinephrin in a concentration of 1:330,000,000; if severe clinical symptoms and unconsciousness are produced by carbon monoxid in a concentration of 15:10,000 and the exhaust gas of automobiles is known to contain from 4 to 12 per cent (400:10,000 to 1,200:10,000); if unconsciousness can be produced by benzol in a concentration as low as 3:100,000 and death by benzol fumes in amounts that defy calculation, the assumption that the ever-increasing quantities of toxic substances which vitiate the atmosphere should be without effect on the body welfare may be dismissed as preposterous. In America alone, according to official data, the total number of gasoline and benzol driven vehicles has increased from 1,000,000 to nearly 9,000,000 between 1912 and 1920, and it is impossible even to estimate the increase of combustion products from private houses, factories, trains and docking steamers. While the increasing use of tractors in agriculture may help to account for the increasing cancer rate in rural communities, the findings of Broders (1919 and 1922) in a study on 2000 cases of epithelioma of the lip have exonerated the farmer's pipe from being a cause of cancer. Broders proved conclusively that "the percentage of tobacco users and non-tobacco users is practically

* Fabrikoid is the commercial name of the rainproof material used for making the folding tops of automobiles.

the same;" among 500 men who were free from malignancy but used tobacco 38.03 per cent smoked pipes and 59.04 per cent cigarettes, whereas of 537 patients with epithelioma of the lip 78.48 per cent smoked pipes and only 1.16 per cent smoked cigarettes; and "in the inoperable cases, the non-tobacco users reached as high as 90.76 per cent". The influence of the age and of the heredity factor should be recalled in this connection; these factors have already been discussed (Chapter VIII, 2 and Chapter V, 194).

When the causes of the acknowledged increase of cancer are the object of research, the following factors deserve consideration: the ubiquity of the combustion products of fuel; the deleterious effects on the body of many of these products; the minute amounts in which they are capable of damaging the organism; the insidious onset and the diversity of the initial stages of chronic intoxication by coal derivatives; and the diminutive size of the body cells, which makes them respond to infinitesimal stimuli even under normal conditions.

Thus far, the bearing of these factors on the cancer problem has failed to be appreciated. Workers in cancer research have given little thought to the influence of combustion products on the incidence of cancer; with the exception of two British pioneers in this field, C. H. Ross and C. E. Green. The inquiry of Ross into the causes of the so-called pitch cancer of briquette makers, as well as his previous investigations, explain the findings of Green. It is to Green, however, that the honor belongs of having been the first to trace the connection between our ordinary, every-day chimney smoke and the cancer problem; the basis of his study and the methods he used are unique in the history of cancer research. The observations in this country of R. H. Green, emeritus professor of surgery of Fordham University, on the disturbances of sulphur metabolism in malignancy, also tend to throw light on the relation of the combustion products of fuel to the development of malignant growth. The work of these three men, which will be discussed in detail, but especially the new train of thought suggested by C. E. Green, has been the foundation of my study on the relation of combustion products to the mortality and morbidity from cancer in Rochester, Minnesota, between 1907 and 1921.

The investigations of Ross.

A long series of experiments, published by Ross in the McFadden Researches (1911-1913) showed that a heterogeneous group of chemical substances induce cell proliferation. To these substances Ross gave the collective name of "auxetics". He classified them under two headings: "natural auxetics", contained in the watery extract of animal and plant tissues, and, "artificial auxetics", contained in the watery extract of coal tar, pitch, soot, petroleum, vaseline, and middle and heavy tar oils. It may be of chemical interest and of value for the better understanding of the cancer problem to give a list of these substances which promote cell division, in the order in which Ross used their aqueous solutions in his investigations:

Natural auxetics: hemoglobin, guanidin, creatin, creatinin, xanthin, methylamin, glycocol, leucin and tyrosin.

Artificial auxetics: benzamidin, theobromin, theophylin, acetamidin, caffein, allantoin, saccharin, ethylamin, propylamin, isobutylamin, asparagin, glucosamin, metaphenylene-diamin, betain, and tetramethyl ammonium hydroxid.

Experiments proved that, although most of the auxetics induced cell division by their mere presence, some of them needed the assistance of another group of chemical bodies, found chiefly among the alkaloids, to which Ross gave the name of "kinetics". The kinetics did not stimulate cell division, but they increased the action of the auxetics as much as five-fold. Certain substances, moreover, were found to combine the properties of kinetics and auxetics: for example cholin (trimethyl-hydroxyethyl-ammonium hydroxid) and cadaverin (pentamethylene diamin), both basic substances, which could be extracted from some vegetable and many animal tissues as they are the products of putrefaction and cell death. These observations were substantiated to a striking degree by Ross' findings during his analysis of the causes of pitch cancer among the briquette makers of South Wales.

It had long been noticed that the men who ground the pitch used in briquette making at Cardiff showed a high incidence of epitheliomas and generalised cancer, whereas those who did the same work at Whitehaven appeared to enjoy immunity from malignant conditions. A government inquiry conducted by Ross (1917) revealed that the pitch used at Cardiff was made chiefly from gas tar, the residue of the soft, bitumous coal employed in the gas works and coke ovens in England. The pitch used at Whitehaven, on the contrary, was derived from blast-furnace tar, which passes over at much lower temperatures and which is made from hard, Scotch coal. Gas tar was also found to produce warts and epitheliomas on the hands and arms of the men who came in contact with it, but the incidence was much lower than for pitch or soot: a fact which Ross explains by pointing out that pitch is practically "concentrated tar". Blast-furnace tar, on the other hand, appeared to be harmless.

Ross was able to prove that the degree to which cell proliferation is stimulated by coal derivatives, such as pitch, soot or tar, depends on the relative amounts of auxetics and kinetics which these derivatives contain. A 10 per cent aqueous extract of gas pitch or gas tar both contain a high percentage of auxetics and kinetics, thus furnishing the combination which incites cell division most effectively: this combination occurred in the material used at Cardiff, where the incidence of cancer is high. The concentration of auxetics and kinetics, however, is lower in tar than in pitch. The blast-furnace pitch used at Whitehaven contains only traces of kinetics, which do not further cell division, and the "auxetics could only be demonstrated" when their action was "artificially augmented by an alkaloid, such as atropin". Blast-furnace tar could not be shown to contain either auxetics or kinetics, but soot always had a high percentage of both kinetics and auxetics; a fact, which according to Ross, explains the high mortality from cancer among chimney sweeps. Attention has been called to the probable reabsorption of soluble coal derivatives from the skin (Chapter XI, 67).

In coal, as further investigations showed, the concentration of auxetics and kinetics is so low that the presence of these substances could only be demonstrated by making the aqueous extracts ten times stronger than for tar. It is well known that the incidence of cancer among coal miners is also remarkably low.* Hard coal contains practically neither auxetics nor kinetics, but the values are higher in proportion to the softer, more bitumous quality of the coal. Soot is also set free in far greater quantities during the process of burning of soft coal, than from anthracite or other hard varieties; and the soot collected from domestic chimneys proved to be particularly noxious, whereas the so-called sut, that is the soot from high temperature and pressure furnaces was found to be much less harmful.

These findings led Ross to conclude, "Cell division is not due merely to an instinct on the part of the cells themselves, but to specific chemical agents, all of which appear to be amino-substances set free by cell-death". A highly interesting link between the life of the present day and that of prehistoric times is furnished by the work of Ross; two factors, both playing a prominent part in the development of malignancy, are thus brought together, namely chronic suppuration, the residue of blood and tissue cells that died but yesterday, and coal derivatives, the remains of vegetable cells that perished millions of years ago. Ross found himself compelled to admit, however, "Malignant invasion, judging by clinical evidence, seems due to some additional factor". It does not seem probable that this "additional factor" could be sught but the body chemistry, which determines the chemical composition of the blood and controls cell activity as well as cell disintegration. The recent investigations of Grove and Vine (1921) support this deduction: Grove and Vine showed that ulcerating varicose veins, which are as a rule refractory to any method of treatment, can be induced to heal with sur-

* It should be noted that the statistics showing a low mortality from cancer among coal miners were compiled chiefly between 1892 and 1912.

prising rapidity by oral administration of dessicated parathyroid substance in doses of one-tenth of a grain for several weeks; they also proved that the ulcerative condition is the result of mismanagement of calcium metabolism, revealed by abnormally low values for ionised calcium in the blood. Hence the work of Ross may be said to constitute an indirect, and possibly unintentional, vindication of the conception of malignancy as a disease of metabolic origin.

The investigations of Green.

Two unusual features, unique in the history of cancer research, characterize the investigations of Green; they were conceived and conducted by a layman, and they were based on the reading of a detective story. The value of the work and the original lines of thought along which it developed may be judged by the synopsis of his findings. His conclusions concerning the parasitic origin of malignancy, which he attributes to mytozoa (slime moulds) may be questioned; but the importance of the data which he collected remains unaltered even when parasites are ignored altogether. His observations have revealed new aspects of the cancer problem; they are a valuable contribution to cancer research.

Green refers to himself as "a former student of medicine" in the first edition of his book, The cancer problem, - a statistical study (1914) - but circumstances apparently prevented him from embracing the medical profession. He is the author of a number of encyclopedias, comprising many volumes on botany, economics, Scotch law and similarly diversified subjects. The fact that he was elected to be a member of the Royal Society of Edinburgh speaks for itself.*

The purpose and the starting point of his study are narrated by Green in these words: "The following pages are written in the hope that they may

* The Royal Society of Edinburgh was chartered 1781; it developed from a society founded 1771. It contained originally a scientific and a literary section which counted Robertson, Hume, Burke, Meade and Hutton among its Fellows. Its present membership list is 600, including twenty British and thirty-six foreign honorary Fellows. Its library contains 50,000 volumes and is considered the most complete scientific library in Scotland. Most of its members are also Fellows of the Royal Society of London. Its president at this date (1920) is professor F.O.Bower, M.A.; D.Sc.; LL.D.; F.R.S.

throw some light on the sphinx-like riddle of malignant disease . . . . Some years ago, after reading one of Conan Doyle's Sherlock Holmes stories, it occurred to me that if some of the World's great problems were attacked in a similar fashion good might result. As a former student of medicine the cancer problem at once occurred to my mind and in a very short time I was in the grip of an enthralling if somewhat gruesome hobby. For the past five years I have endeavored to collect every piece of evidence, which seems to bear upon the problem of malignant growth in the hope that a clue might be got to the cause and possibly to the cure of the condition."

The evidence thus collected by Green has been gathered with that truly Scotch thoroughness which leaves no stone unturned; the statistics which he presents are those of the Registrar General of England and Scotland; the elements of error which cling to statistical data of any kind are given careful consideration; the topographic factors to which he calls attention have been analysed in detail as Green "motored over practically the whole of Scotland in the endeavor to find a clue", when the evidence obtained appeared to be conflicting. The information secured by the study of conditions and factors bearing on the cancer rate in Scotland and England has been checked and found to be corroborated by the analysis of similar conditions and factors in France and in the Orkney Islands.*

The deductive line of reasoning used by Green in his investigations led him to inquire successively into (1) the causes of tumor formation in plants, (2) the occupational incidence of cancer, (3) the effects of local topographic conditions on the cancer rate in different localities, and (4) the influence on the mortality from malignant disease of combustion products and of different types of fuel. How these very dissimilar fields of research came to be selected through a process of logical association of ideas, how findings in one field suggested questions and possibilities with regard to the next field, and how the data

* The findings in France and in the Orkney Islands are given in the second edition (1917), in which, unfortunately, the introductory passage that has been quoted has been omitted and the material so rearranged as to hide the ingenuous use which Green made of the deductive methods employed in criminology. The original sequence of thought of the first edition has been adhered to in this synopsis.

concerning plant tumors became the basis of an investigation concerning the smoke nuisance and the cancer incidence in diverse countries, cities and rural communities, is shown by Green's arguments and observations, which may be briefly summarised as follows:

1. It is known that tumors on plants are a common occurrence where the soil is rich in sulphur or where artificial manure, requiring the addition of sulphuric acid during its manufacture, is used extensively. Tumor growth is rare in plants when the soil contains a high percentage of lime and can be prevented by the artificial introduction of lime into the soil according to the data of the Bureau of Agriculture's "Official leaflet, No. 77". Therefore, sulphur and sulphuric acid may be said to promote and lime to combat the development of plant tumors. Does the occupational incidence of cancer furnish any clue indicating that sulphur and lime have a similar effect on malignant conditions in human beings?

2. Statistics show that the mortality from cancer is highest among chimney sweeps and lowest among paper-makers and tanners. Paper-makers use great quantities of sulphuric acid in their trade, but both paper-makers and tanners also come into daily contact with enormous quantities of lime. Statistical data concerning other industries, in which sulphuric acid alone is used, do not show a high cancer incidence. The low mortality from cancer among tanners suggests, however, that lime antagonises malignant growth in man as well as in plants. The high mortality from cancer among chimney sweeps, on the other hand, suggests that although the sulphur in sulphuric acid does not further the development of malignancy, the sulphur compounds in combustion products, such as soot and smoke, might pave the way for malignant disease. Does the local incidence of cancer furnish any evidence that combustion products affect the cancer rate?

3. Analyses of the local incidence of cancer and of the local topographic conditions prove that local topography is a factor, which does influence the mortality from malignant disease. Towns and suburbs situated in hollows or

cups, between hills, and presenting an irregular roofline, high and low buildings being unevenly distributed, have a high cancer rate; whereas towns and suburbs built on flat sites or on the edge of the aforementioned cups, and presenting an even roofline, the height of all the buildings being practically uniform, show a low mortality from cancer. For example: in London the district of St. Marylebone has the highest cancer rate (17 per cent); this district is situated in a hollow, it has an extremely uneven roofline, being composed of a haphazard conglomeration of large and small buildings. Stepney, another district of London is situated on the edge of a cup, it consists almost entirely of the same type of two-storied houses, its roofline is very even in consequence: the cancer incidence is the lowest in the whole city of London (1.84 per cent). Glasgow is a large industrial center, but it possesses a surprisingly even roofline, and it is windswept because of its situation on the Clyde; "the site, especially towards the east and the south, is very flat, as it is also on the north along the side of the river. . . . . One or two parts of the center of the city of Glasgow, however, are slightly hilly. . .": the mortality from cancer is remarkably low (2.98 per cent).* Comparative tables containing topographic details and statistics on the cancer rate in most towns and villages in England and Scotland show the relation between local topography and the cancer incidence to be uniform. It is obvious that combustion products, especially smoke, will be dispersed and carried away in localities that are either windswept or situated in flat surroundings, but that they will be retained and "hang around" in cups and hollows and where "streets of sky-scrapers alternate with rows of small houses" since the resulting formation of cul-de-sacs will prevent their proper elimination. These facts suggest that the retention of combustion products somehow promotes the development of cancer. The history of a so-called cancer house supports this deduction. The house could not be leased on account of the bad reputa-

* This is particularly noteworthy as according to Hoffman's International Statistics of Cancer Mortality (1908-1912) Scotland ranks third in cancer rate among the countries of the world included in these statistics, the deathrate from cancer being 103.0 for each 100,000 population. The percentage values given by Green refer to "the proportion of cancer deaths to deaths from all other causes".

tion which it had acquired through the occurrence of a number of deaths from cancer within its walls. It was situated at the bottom of a steep and tree-clad slope, a fact, which as Green points out, undoubtedly furthered the retention of combustion products. It was pulled down and a house with a much higher roof and taller chimneys was erected on exactly the same spot; the possibilities for elimination of the combustion products were much greater by the character of the new building and the inmates remained free from cancer. "One swallow, however, does not make a summer; and whether there are cancer houses or not (says Green) the question does not lie, to my mind, so much with the house as with its surroundings". But if the inadequate elimination of combustion products affects the cancer rate, as it seems to do, might not the type of fuel prove to be an important factor?

4. Cancer is unknown in Iceland and Greenland where animal oils are used exclusively for heating and cooking purposes. The survey of conditions in Scotland and England shows that districts in which wood and turf (peat) are burnt principally have a low incidence from cancer, whereas districts in which coal is the staple fuel have a high mortality from cancer. Do these findings apply to other places, as well as to England and Scotland?

The foregoing outline illustrates the method of reasoning followed by Green. Some details about his investigation of conditions in France and in the Orkney Islands are of interest, because they reveal the means which he used to collect his evidence. The original numerous maps, diagrams, tables and photographs, including a picture of the cancer house, are given to support his contentions.

The mortality from cancer in France was studied by Bertillion, the originator of the finger-print system (1911) and published by him in diagramatic maps of the country. Green secured a set of these maps and wrote a letter to each prefect of the eighty-seven French "departments", asking for details concerning the fuel used in the district. He received a courteous and detailed reply in every instance. The data thus obtained were now superimposed on Bertillion's maps and the result proved that the highest cancer rates found by Bertillion occurred where coal was used exclusively, and that the incidence of cancer was low where wood was the staple fuel. Four maps of France, showing that these findings apply to rural communities as well as to towns, are given in the second edition of Green's book.

The Orkney Islands were selected for study because the percentage (5.32) of deaths from cancer as compared with deaths from all other causes differs but little from the percentage for the whole of Scotland (4.23); because only a few islands at which ships call regularly burn imported coal and the others, which are practically cut off from intercourse with the mainland, burn the native peat, while none of them possesses any wood. The inhabitants are farmers or fishermen and there are no industries to confuse the issues.

In the main the analysis of the relation between the cancer rate and the type of fuel used confirmed Green's previous observations: islands in which peat was used exclusively had a low mortality from cancer, those using coal a high mortality. There were, however, a few startling exceptions. Three districts in which nothing but peat was burned had a high incidence of cancer. This puzzled Green considerably until it occurred to him that there "might be peat and peat". He sent for samples of peat from all the peat-burning islands of Orkney and from various districts in Scotland and had their total sulphur content determined by a chemical laboratory. The results of this analysis were surprising and interesting. Tables in which the percentage of sulphur in the peat of a given district and the cancer rate of the same district were put down side by side proved that cancer was unknown where the sulphur content of the peat did not exceed 0.10 to 0.12 per cent, it was comparatively rare when the peat contained 0.23 per cent, and it was "very common" when it contained 0.75 to 0.89 per cent. Moreover, samples of peat (from three "purely peat-burning" districts, where cancer accounted for one death in eight to eleven deaths from other causes) "handled like coal, were hard and stony in appearance, and, when burned, crackled like coal and gave out long blue flames totally unlike ordinary peat fuel, which simply smoulders and glows. . . . . . Although the product of a peat bog, it approached coal in character and had a high percentage of sulphur. It was the only fuel used in Birsay", (one of the three districts of Orkney in which the cancer rate was high).

These findings suggest that the mortality from cancer is influenced and increased by the total amount of sulphur contained in the fuel, as well as the type of fuel which is used chiefly in a given district.

The researches of Greene and Killian on sulphur metabolism in malignancy.

The views expressed by R. H. Greene in his book, "Cancer, its nature, diagnosis and treatment" (1918), are the result "of the labors of a surgeon and a physiologic chemist, working together for the past few years". The observations were made at the House of Calvary for Cancer. Greene's conclusions are, that the basis of all successful treatment of malignancy "is to be found in measures which tend to increase tissue metamorphosis". Only such findings as deal with the metabolism of sulphur in malignant disease will be considered here.

Sulphur metabolism still presents innumerable problems, although numerous investigations (a few of which will be discussed at the end of the paragraph), have been carried on since 1916, when von Fürth and Matthews emphasized the limitations of our knowledge on the subject. It has been proved conclusively, however, that sulphur metabolism is intimately connected with and part of protein metabolism. This fact alone opens up many vistas with regard to the relation of disturbances of sulphur metabolism to the cancer problem.

According to MacLeod (1920), "A knowledge of protein chemistry has come to be essential in practically all branches of medical science". To the majority of medical men, however, chemistry with its complicated formulas appears to be chiefly "a weariness of the flesh and a vexation of the spirit". Yet chemical formulas are needed to visualise the changes which take place in chemical reactions, and chemical reactions are essential factors in all metabolic processes, and often of vital importance to the owner of the body in which the reactions occur. A brief outline showing the relation of sulphur to protein metabolism in which a few chemical formulas are presented in such a way that they will be easily recalled, may prove convenient and useful for the appreciation of the findings of Greene and Killian.

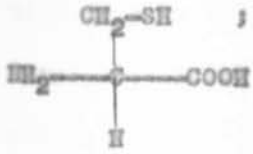
It is known that there are "eighteen different amino acids concerned in the constitution of the protein molecule, but they are all alike in the characteristic structure" (MacLeod). This characteristic structure is represented by the following basic formula given by MacLeod:

$$\begin{array}{c}\text{(any radical)}\\ | \\ NH_2\text{——}C\text{——}COOH \\ | \\ H\end{array}$$

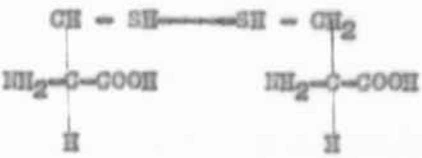
The simplest amino acid is glycin or glycocoll in the formula of which a single hydrogen atom (H) occupies the place of "any radical"; the structural formula of glycocoll is, therefore,

$$\begin{array}{c}H\\ | \\ NH_2\text{——}C\text{——}COOH \\ | \\ H\end{array}$$

. It may be observed that this formula bears a curious resemblance to a mariner's compass, when the central carbon atom is compared to the pivot on which the magnetic needle swings, the NH_2 (amino) group to "West", the COOH (carboxyl) group to "East", and the two hydrogen atoms to "North" and "South". The comparison, childish as it may seem, will be found to be of practical value when an attempt is made to recall the formulas concerned in the relation between sulphur and protein metabolism. For, if a hydrogen atom is replaced by a CH_3 (methyl) group, the formula of another amino acid, alanin, is obtained and more easily remembered. "The other amino acids may be considered as derivatives of alanin" (MacLeod). If one H of the CH_3 group in alanin is replaced by an SH group, one of the two sulphur containing fragments of the protein molecule is represented, namely cystein



; and two molecules of cystein attached together by their SH groups, like Siamese twins, furnish the formula for the other sulphur-containing amino acid, cystin, which will thus be recalled without difficulty:



Cystein and cystin are the only two amino acids which contain sulphur and "it is in protein alone that sulphur is usually taken into the animal body" (MacLeod).

Whereas the sulphur intake is thus dependent on the protein intake in the food, the sulphur output is controlled by two factors, namely: the protein intake and the disintegration of the body proteins, the tissues. The total sulphur output is composed of two kinds of sulphur compounds, namely sulphates or oxidised sulphur (80-85 per cent) and neutral, unoxidised sulphur; the sulphates are present in two varieties, such as inorganic sulphates and ethereal (organic) sulphates.

The inorganic sulphates are derived entirely from the food, they decrease during starvation. The ethereal sulphates, on the other hand, are derived from the food and from the destruction of body protein, they are products of both exogenous and endogenous metabolism; during starvation or tissue disintegration the portion of the ethereal sulphates derived from the body proteins naturally increases. The ethereal sulphates are combinations of sulphur with aromatic compounds and with potassium salts. The mismanagement of potassium metabolism in malignancy to which several investigators have called attention (Chapter V, 116-118), may prove to play a part in the abnormalities of sulphur metabolism in malignant disease, although so far as I know, this possibility has not yet been considered.

The neutral, unoxidised sulphur is derived entirely from the tissue proteins; it is altogether a product of endogenous metabolism. It is obvious from these data that "the excretion of sulphur therefore runs more or less parallel with the intensity of protein metabolism" (MacLeod).

Marked disturbances of sulphur metabolism in malignant disease, revealed by urinalyses alone, have been reported by many investigators. Kahn (1917) has published an excellent summary of these observations. He comes to the conclusion that, although anomalies in the excretion of sulphur may occur in nonmalignant conditions, the determination of the colloidal nitrogen in conjunction with the Salomon-Saxl test for neutral sulphur "is of great aid in the diagnosis of carcinoma, if both tests are positive".

The investigations of Greene and Killian (1918) are based on analysis of the sulphur content of both blood and urine. The Salomon-Saxl reaction proved to be unreliable "because in all conditions the hydrogen peroxid (used in the test) did not completely oxidise the neutral sulphur; and . . . . it was found difficult to obtain a sample of hydrogen peroxid which did not contain an impurity that would give a precipitate with the barium chlorid". Greene and Killian therefore adopted the Benedict method for total sulphur and the Folin technic for total and inorganic sulphates. The findings of Greene and Killian may be summarised as follows:

In malignant conditions the total sulphur content of the blood is increased, notably the amount of neutral, unoxidised sulphur; but the sulphur output in the urine is decreased, although the same preponderance of neutral sulphur prevails, the values being "from 20 to 30 per cent or even higher", instead of the normal 5 to 13 per cent. Treatment with roentgen rays greatly increases the output of neutral sulphur in the urine, which returns to its former level, however, as soon as the treatment is discontinued. Surgical removal of the tumor is "apparently accompanied by a proportionate drop" of the excretion of neutral sulphur. The effect of radiotherapy and surgery on the neutral sulphur content of the blood is not discussed, which is to be regretted. For, although tissue catabolism may account for the high sulphur content of the blood before treatment and for the increased elimination of sulphur in the urine resulting from the disintegration of cells by the roentgen rays, it does not explain the initial, reduced output of sulphur in the urine, nor the preponderance of neutral sulphur in the urine and in the blood. These findings point to a fundamental derangement of sulphur metabolism, to an inability of the organism to oxidize its sulphur.

Lewis (1920) suggests in his studies on sulphur metabolism that the retention of sulphur may be "in response to a specific demand by the organism"; he was able to show that the addition of cystin to a diet of casein, which is low in cystin, preserves the nitrogenous balance in dogs. Robin (1920) found the sulphur content far below normal in the carcinomatous portions of the liver in five cases of hepatic cancer. Whereas the observations of Greene and the findings of Robin both support the conception of Lewis, that sulphur retention might be a defensive measure of the organism, the increased amounts of neutral, unoxidized sulphur also suggest the possibility of exhaustion or inefficiency of the organs concerned in the oxidation of sulphur. It is obvious also that overworked as well as inefficient organs are apt to break down under any additional strain. Prolonged exposure to combustion products which are rich in sulphur may be expected to tax the sulphur metabolism rather severely; because the sulphur having entered the body either by inhalation or by contact with the skin, must be eliminated somehow. The use of sulphur-containing ointments shows that sulphur can penetrate through the epidermis; the peculiar "taste of sulphur" experienced after travelling in the underground railway in London before the trains were electrified, or after passing through long railway tunnels, is a matter of common observation. Determinations of the sulphur content of blood and urine during the therapeutic use of sulphur containing ointments might throw some light on the many problems of sulphur metabolism and explain, in part at least, the relation between the sulphur content of fuel and the incidence of malignant growth observed by Ross and C. E. Green and the anomalies of sulphur metabolism reported by Green and Killian. If, as Lewis says in his conclusions "cystin is essential for maintenance as well as for growth" according to the evidence furnished by his experiments, imperfect elimination of this sulphur-containing amino acid in the form of the so-called neutral sulphur might also further the undue proliferation of cells in malignant growth; since "The problem of cancer is but one aspect of the broader problem of growth". (Benedict and Rahe,1917).

Further data concerning the relation of combustion products to the cancer problem.

The vast statistical researches of Hoffman (1915) published under the title, "The mortality from cancer throughout the world", reveal a steady increase in the incidence of malignant disease in all countries. Hoffman gives the following summary of his findings:

"1. The menace of cancer throughout the civilised world is far more serious than is generally assumed to be the case.

"2. The mortality from cancer is increasing at a more or less alarming rate throughout the entire civilised world; this increase implies most serious consequences, present and future, to the populations concerned.

"3. Practically all forms of cancer are on the increase.

"4. The cancer frequency decreases with diminishing distances from the equator.

"5. Even a very low cancer death rate is not necessarily evidence of the intrinsic untrustworthiness of the returns."

It is of interest to note that, according to Hoffman's statistics, which are the statistics of The Prudential Insurance Company of America,* the frequency of cancer diminishes the nearer we come to the equator; that low cancer rates are not necessarily evidence of untrustworthy data and that the arctic re-

* Frederick L. Hoffman has been the statistician of the Prudential Insurance Company of America for a very great number of years; he is also one of its vice-presidents. He holds the position of Chairman of the Committee on Statistics in The American Society for the Control of Cancer; the degree of LL.D. was conferred upon him by the University of Oxford.

gions are free from cancer. The latter observation has been confirmed by Stephanson (1919) during his long sojourn in these regions. Ross (1919) has suggested that the absence of cancer in the arctic regions is to be explained by the inability of microorganisms to exist and survive in extremely low temperatures. The ravages caused among the Eskimos by tuberculosis and measles according to the observations of Stephanson would seem to contradict the conception of Ross, and to furnish an argument against the parasitic etiology of malignant disease. The vast, wind-swept arctic plains are, on the other hand, likely to be singularly free from the combustion products of fuel.

Although there are great coal deposits in the far North, "some of this coal is of good quality and is readily accessible" (Stephanson), very little coal is used as fuel. During the past thirty years, the driftwood which had accumulated for centuries has been the staple fuel of the Eskimo, even after he abandoned the warm, well-ventilated, earth-covered type of dwelling of his forefathers and began to adopt the flimsy imitation of the white man's house. The original native dwellings could be heated effectively with the native walrus-oil lamps, but the ambitious and useless modern structures cannot be heated in this way. As the result, "the modern Eskimo house is practically hermetically sealed against fresh air. If there is a key-hole in the door, you will find it stuffed with chewing gum" (Stephanson). According to the great arctic explorer the high death rate among the Eskimos from tuberculosis is the immediate result of their changed mode of living. The contradictory findings and the arguments for and against an indirect relation between a predisposition to tuberculosis and to malignancy have already been discussed (Chapter VIII). There is little doubt however that ill-ventilated houses offer a splendid opportunity for the retention of combustion products. An experience with coal gas in a snow house, to which Stephanson refers as "the narrowest escape from death we had on our entire expedition" is of interest because the prevailing conditions may be duplicated without difficulty in any type of house, and are likely to be found in many rural communities, in any except a tropical climate in which the population generally lives more or less in the open air. Stephanson describes the incident as follows:

"We had found no fuel that day (travelling towards Victoria Island) and to save ourselves the trouble of making camp we moved into an abandoned snow house. . . . . A new camp is much warmer than an old camp, for a new snow house is a snow house, but an old one is an ice house. This particular one had evidently been kept pretty warm by its former occupants, for its walls were solid, glistening ice. We were all warm from fast travel and in our hurry to get the camp heated up we closed the door tightly*. . . . The cooking was my job that night and I had set the primus stove (burning coal oil) on a block of ice and was on my knees cutting up snow into the kettle to make water. Tannaumirk and Natkusiak were talking and joking as usual. In the midst of one of his funny stories, which he told with a good deal of pantomine, Tannaumirk all at once threw himself backward on the bed (a bed-platform) and made gurgling noises. All of us thought that these actions and gurglings were part of the pantomine accompanying the story; still I asked Anderson to look and see what Tannaumirk was up to, for he did not get up again as quickly as we expected. When Dr. Anderson turned to look, he fell face forward on top of Tannaumirk. I knew then in a twinkle what was the matter, for it was that we were being poisoned with coal gas, which is so insiduous a thing that under ordinary circumstances one does not notice its presence. Natusiak, to whom the phenomenon was a strange thing, saw nothing to be alarmed at, and when I told him immediately to break a hole in the snow wall back of where he was sitting, he went about it with great deliberation. Fortunately, in order to make the hole, he had to reach up after his knife which he had stuck into the wall. When he tried to rise he found himself unable to do so and that scared him so that with his last

* In a snow house a hole in the roof permits the escape of smoke, but unless the "door", a mere loose block of snow, is taken from the entrance aperture, there is little ventilation. Some types of Eskimo houses are entered by a long alleyway, the "door" never being closed all winter, "so that a current of air circulated through the house at all times". (Stephanson).

strength he threw himself back against the wall and broke away the loose block of snow by which we had, a few minutes before, closed the door. He then crawled out on all fours, but was too weak to stand up. I followed him out and had strength enough to stand up after getting out, but it was only for a moment and I fell down beside Natkusiak. It was a calm, starlit night, with the temperature about 45 below zero, and the situation was evidently serious, for all of us were lightly clad. . . . . It must have been fifteen minutes that we lay flat outside the snow house before Anderson's face appeared at the hole in the wall. His mind was clear apparently, but he had no realization of what had happened and asked us in a querulous voice what we were doing out there and why we had put out the stove and let the cold air into the house. Before I had time to answer him, however, he realised what had happened and crawled out and started walking about and drawing into his lungs as deep breaths of air as possible. He soon found, however, as I had found a few minutes before that this was the worst possible thing to do, and had to stretch himself out flat on the ground like the rest of us. It must have been another ten minutes until Tannaumirk also came to his senses and crawled out. . . . He had been much worse affected than the rest of us and while we were able to think clearly his mind was evidently in a fog. . . . After walking around the camp in a circle two or three times he started straight off somewhere. . . . he said later that either he was unable to see the camp or else he did not have the sense to recognise it when he did see it. . . . An hour later (after Stephanson had fed his companions with their last "emergency" can of malted milk) the three of us were feeling comparatively fit again and next morning we noticed no ill effects, but Tannaumirk was sick not only that night but also the next day. Of course our trouble had been from closing the house too tightly. Looking back upon our various experiences with primus stoves in the past, I can see now that we must many a time have been near a similar outcome before."

An ice house in the arctic regions is certainly the last place and a primus stove the last source to be suspected of furnishing carbon monoxid, in sufficient amounts to produce a severe form of acute poisoning. Poorly trimmed kerosene lamps used for lighting purposes are not likely to be suspected either as sources of carbon monoxid production yet the letter which I received from a farmer in Wisconsin, who asked if the headaches and nausea experienced by all the members of his family as soon as their kerosene lamps had been burning for a couple of hours could possibly be connected with coal gas poisoning. Stephanson's experience strongly suggests such a possibility and the extreme lassitude on waking next day which this family also complained of is a typical symptom of chronic carbon monoxid poisoning and would seem further evidence that the lamps were at fault, since the writer of the letter commented on the fact, that their stove did not seem to make them feel miserable, when it was burning, but the lamps had not been lighted.

It is by no means suggested that either combustion products or their carbon monoxid content alone are the only factors in civilised life which further the development of malignant growth. They may prove to be an important factor, however, by reducing the efficiency of one or more of the endocrin glands, the regulators of the blood chemistry. It is well known that functional anomalies of certain endocrin glands cause marked chemical changes in the composition of the blood, the staple food of the body cells. The minute insults to which the cells are subjected daily by chemical anomalies in their blood supply are likely to affect them as much in the long run as the grosser chemical insults inflicted by analin dyes or the mechanical injuries produced by various types of "chronic irritation": both analin and chronic irritation are admitted to further the development of malignant growth.

The human body is endowed with almost miraculous powers of recuperation. Nassauer has called attention to the fact that typical anilin cancers take, on an average, fifteen years to develop and have been known to take as long as twenty-eight years. He also points out that cancer of the bladder is frequent not only among the workmen who are employed in the manufacture of anilin, but in persons living in the vicinity of the dye works and who are in no way connected with the factory. It is hardly to be expected in view of these findings that malignant conditions referable to the secondary effects of chronic carbon monoxid poisoning should become manifest in a short space of time. But the increasing amounts of carbon monoxid and other combustion products with which the air in civilization is polluted daily, the parallel and acknowledged increase of cancer in the civilized world, the absence of cancer until now in the arctic regions, and its increasing frequency with diminishing distance from the equator certainly furnish food for thought. It is obvious also that any cell or group of cells which has been previously damaged, no matter whether the lesion be demonstrable or beyond perception, will resent chemical anomalies in its blood supply far more than cells which have remained entirely free from injury; this may help to explain the different localisations of malignant growth.

The following data give a rough estimate of the increase of combustion products in the past ten years, during which the increase of cancer has been commented on in every country. The statistics of the automotor industries show that the number of motor-driven vehicles in America alone has risen from 1,000,000 to close to 9,000,000 between 1912 and 1921, according to "the revised total registrations after careful checking with the final records of the various secretaries of state". Teague has shown that the exhaust gas of motor vehicles contains from 4 to 12 per cent of carbon monoxid (Sayers). Henderson considers it "fatal for a man to breathe for an hour air which is normal in every respect but which contains as much as 0.4 per cent of carbon monoxid". The exhaust gas produced by motor vehicles is, fortunately, diluted and carried away to a great extent by air currents. Yet even the most casual observer has seen in the wake of passing automobiles and trucks trails of bluish smoke which are visible for many minutes and extend for several hundred yards on wind-still days; nor can the odor of exhaust gas which is then perceptible have failed to attract attention. The characteristic odor of exhaust is not caused by carbon monoxid, an odorless and colorless gas; it is the result of other combustion products but the odor proves that the amounts of carbon monoxid mentioned by Teague are being poured into the air simultaneously.

The use of illuminating gas for cooking and heating purposes alone has increased no less than 60 per cent since 1914 (Wilmer). Illuminating gas made from coal contains from 5 to 10 per cent of carbon monoxid; producer gas contains about 25 per cent and carburetted water gas as much as 30 per cent. Seventy-eight per cent of the gas used in the United States is water gas (Wilmer). Yarrow reported (1900) that he had made a careful investigation of leaky gas fittings and found "that it is the exception rather than the rule to find them perfect in our houses". The investigation of the U.S.Bureau of Mines (1920) proved that three out of five types of gas tubing in common use are unreliable and dangerous, and that two out of four varities of gas tubing connections are equally unsatisfactory, leaks being frequent (Winters). Few persons attach any significance to "a faint smell of gas"; yet it is this faint odor which heralds the minute traces of carbon monoxid that are so often the cause of chronic carbon monoxid poisoning.

The production of carbon monoxid is inversely proportional to the rate of burning of fuel. The blast in the steel industry produces 26 per cent of carbon monoxid (Wilmer). The temperatures required for the manufacture of steel greatly exceed those needed for the heating of houses or the cooking of food; the carbon monoxid content of domestic chimney smoke is therefore likely to exceed that of the steel furnace blast. The exact percentage of carbon monoxid in chimney smoke does not seem to have been made an object of study, but the findings of Harris (page 66) prove that ordinary chimney smoke can produce acute and severe carbon monoxid poisoning. It is wholly impossible to form even an approximately correct idea of the amount of smoke which is poured into the air daily throughout the world by domestic fires, factories, trains and steamers, but the Seventh Report (1922) of the Committee for Investigation of Atmospheric Pollution in England furnishes interesting details concerning the city of London during a period of observation of five months. "From the records of the instruments (at the Meteorological Office of the Air Ministry) it would appear that in London domestic fires are responsible for nearly two-thirds of the total smoke"(McAdie). In the same report J. S. Owens is quoted as saying that there is a tendency for the death rate to reach a maximum when the impurity of the air is highest, or rather a little later; although on the whole there is no obvious relation between the actual quantity of impurities and the number of deaths. The apparent contradiction of these findings might be explained by the consideration that metabolic disturbances referable to air pollution are likely to require several years to produce demonstrable symptoms (like anilin cancers) whereas the observations of the Committee only cover a period of several months. The amount of soot produced by domestic chimneys alone in the city of London during one day (6 a.m. to 9 p.m.) has been estimated at 200 tons.

Evidence that the carbon monoxid content of combustion products is capable of disturbing the functional activity of several of the endocrine glands is by no means lacking. Nor does the deduction seem far-fetched that, if total destruction of one of these glands gives rise to a well-known clinical syndrome, the temporary functional incapacity of that gland will give rise to the same set of symptoms in a minor degree, and that the symptoms will be transient and disappear as soon as the gland has recovered sufficiently for normal function. Destruction of the suprarenals, partial or complete is known to produce the syndrome of Addison's disease of which the cardinal symptoms, muscular and circulatory weakness, hypotension, nausea, chilliness, a tendency to fainting spells, sudden exitus from cardiac failure, bronzing and abnormally low blood sugar values may be found enumerated in any text-book on clinical medicine. The sum total of all observations on carbon monoxid poisoning proves that exposure to this gas produces muscular and circulatory weakness, tendency to fainting, sudden death, as well as chilliness, low blood pressure, and transient bronzing and transient but very low blood sugar values (Sayers, McGurn, Luden and others). Nausea and headaches are the commonest symptoms, but the manifestations vary in different persons according to (1) the amount of gas inhaled, (2) the duration of exposure and (3) the relative efficiency of different endocrine glands in different persons. It has already been pointed out (Part I, Chap. V, 113) that, for example, the combination of an inferior thyroid gland with strong, efficient suprarenals is bound to produce a type of body chemistry differing in several respects from that furnished by an active thyroid combined with inadequate adrenal glands. It is only natural that different types of body chemistry should give rise to divergent reactions; no matter whether the reactions be called forth by medical treatment or by an injurious agent like carbon monoxid. It is obvious therefore that certain symptoms of carbon monoxid poisoning will be severe in one but mild in a second person, other signs of intoxication predominating in the latter.

The detailed accounts of fourteen cases of chronic carbon monoxid poisoning published by McGurn (1917) are particularly instructive, because (1) they reveal the dissimilarity of the disturbances which can be caused by exposure to the gas, (2) McGurn discovered the source of carbon monoxid in every instance and was able to eliminate all other factors, (3) there was no personal or family history of disease to complicate the interpretation of the findings, and (4) the patients were all of average intelligence, capable of furnishing detailed information. Two of the histories given by McGurn (Cases 10 and 13) might be quoted as an illustration of the different effects of soft coal smoke on two persons, a man and a woman, who lived in the same apartment-house. The smoke was furnished only for a couple of hours daily by the low chimney of a neighboring factory. Four other persons living in the apartment-house were seriously affected by the smoke, but they recovered much more rapidly.

Case 10: Mrs. ——, housewife, aged forty-three, had always been well and had a naturally ruddy complexion. After living in the apartment she became very restless and irritable, and she was often observed to turn very pale for a brief period. Her appetite became ravenous. At times the pungent odor of the smoke made breathing difficult in her apartment. When examined by McGurn her pulse was regular but fairly rapid; the heart sounds were normal with the exception of a soft systolic murmur. The total urinary solids were diminished by 60 per cent, although the urine was normal in other respects, but the patient's blood pressure, taken repeatedly with both Sandborn and Tycos instruments, was 205 mm. After five weeks' absence from the apartment all the symptoms disappeared and the clinical findings were practically normal: the blood pressure had come down to 155 mm., the pulse had dropped to 70 and normal values were found for the urinary solids. But, after living in the apartment for one month the patient's nervous irritability and all her vasomotory symptoms reappeared and her blood pressure again rose to 270 mm. She was again sent away to spend the summer in the country. During her absence the factory discontinued the use of soft coal and made important repairs in the power plant. As the result the patient's apartment was no longer flooded with combustion products and her health remained excellent. It will be recalled that a voracious appetite, dyspnea, nervous irritability, rapid heart action and high blood pressure are among the characteristic symptoms of thyroid hyperactivity.

Case 13: A merchant, aged forty-one, had always been in excellent health until he came to live in the apartment house. He had been accepted as a class A risk for heavy insurance by two well-known insurance companies only six months prior to his change of abode. After living in the apartment for a few weeks he began to suffer from general indefinite malaise. He was restless and did not sleep well; he felt weak and exhausted, especially on waking (morning languor); his breathing became labored on slight exertion and intense coronal headaches developed. When he consulted McGurn in the latter's office, he mentioned that he had recently begun to pass very large amounts of almost colorless urine. Urinalysis now revealed the presence of 12 per cent of sugar. McGurn being unfamiliar with the patient's living conditions was puzzled by the fact that 12 per cent of sugar should have been overlooked by two insurance companies; he prescribed dietary measures, but the patient sought treatment elsewhere and was lost sight of for two years, at the end of which McGurn was called to the apartment. The smoke from the neighboring chimney was clearly perceptible in the rooms, the patient was in a pitiful condition. The physical findings which he now presented were: loss of weight from 195 to 158 pounds; pallor and anemia; weak heart action; pulse varying from 84 to 100 on the slightest exertion by which the patient is covered with cold perspiration; muscles look shrunken, their strength is greatly impaired; the skin and the flesh are hypersensitive to touch; sensation is impaired in both legs; the plantar reflexes are absent; the right pupillary reflex to light is impaired. Questioning reveals that for the past year the patient has been suffering from numbness and from a sensation of burning in legs and feet, accompanied or followed by sharp, lancinating pains agonizing in intensity, and stabbing pains in fingers, chest and heart. To quote McGurn: "The story of constant suffering, that came from the lips of this man is the most lucid and graphic account of intense mortal anguish that I have ever heard".

At the end of six weeks, spent in a local sanitarium and followed by a change of residence all these symptoms began to subside. The reaction of the right pupil had returned to normal as well as the plantar reflexes; a fact which excludes the possibility of syphilitic infection. Strength and weight had increased; the patient now weighed 175 pounds. After eighteen months he was able to attend to his business, although over-work still caused a return of the pains; on an ordinary mixed diet the urinary sugar did not exceed 2 per cent. McGurn says "Each month in the past eighteen has shown some definite improvement, but that complete recovery seems doubtful"; he adds "The patient, a man of education and a good observer is very emphatic in his claim that exposure to minute traces of coal or illuminating gas or to the combustion products of gasoline always causes him more or less suffering".

A similar hypersensitization to the effects of carbon monoxid is suggested by the experiments of Haldane and Smith on themselves and was also observed by me after my personal experience with chronic carbon monoxid poisoning. Haldane mentions that in his first series of experiments the inhalation of 0.06 per cent (6:10,000) of carbon monoxid "produced no symptoms except shortness of breath on exertion" in several hours. But he adds: "About a year later we tried a similar experiment and found that 0.06 per cent was far too much for us"; and when the experiment was again repeated later, at Oxford, it was found that "even with 0.03 per cent the saturation (of the blood) gradually crept up during four or five hours to over 30 per cent". Haldane explains this phenomenon as evidence of "acclimatization" during the earlier experiments.* Findings which tend to show, however, that the body did not handle one-half the concentration of carbon monoxid as successfully in later experiments as it had handled the greater concentration in the first series suggest hypersensitization as much as acclimatization; they also tend to prove that the oxygen deficit created by inhalation of the "toxic" gas had been resented and "registered" by the body as a whole.

McCombs (1912), on the other hand, who published observations on 1000 cases of acute gas poisoning, reports that workmen who had been employed in gasworks for a great number of years appeared to be in excellent health; these men paid no more attention to a fairly severe degree of gas-poisoning "than most people do to an ordinary headache"; but they had developed a compensatory polycythemia of from 8,000,000 to 10,000,000 erythrocytes. Forbes (1921) mentions a similar instance of a "fire boss" who, notwithstanding prolonged exposure during a fire in a mine lasting eighteen months could still "stand as much gas as most men"; but the erythrocyte count of this man is not given. It is well known, however, that many of the compensatory mechanisms of the body respond more readily in some persons than they do in others, and that such mechanisms eventually break down, when the

* These data are given in a letter from Haldane, quoted verbatim by Henderson.

demands on them are too great or prolonged. It would be of the greatest interest to know the ultimate fate of Forbes' "fire boss".

Nasmith and Harrison (1910) studied the changes induced in the blood of rabbits by living in an atmosphere of water gas. They found that nucleated red cells appeared in the blood of the animals at the end of two days when the concentration of the gas had been increased so that "on the third day about 25 to 33 per cent of the hemoglobin was saturated". (It should be mentioned that accurate methods for determination of the hemoglobin saturation with carbon monoxid were only devised after 1921 by the United States Bureau of Mines.) Rabbits living in an atmosphere of water gas for two months showed interesting changes in their blood counts. The following record of one rabbit may serve as an illustration; numerous counts on different animals showing similar changes are given in the original article.

Blood counts on a rabbit put in the gassing chamber January 4, 1909.

(data of Nasmith and Harrison)

Date	Erythrocytes	Normoblasts Per cent	Leucocytes	Hemoglobin Per cent
January 4.	7,008,000	0	10,000	79
January 8.	6,832,000	28	33,500	79
January 29.	10,704,000	1	4,600	118
February 2.	10,976,000	1	7,300	—

The exhaustion of the hemopoietic system is seen clearly in the great drop of the leucocytes, from 33,500 to 4,600 within three weeks, and in the reduction of the percentage of normoblasts. It was found that no continued overproduction of erythrocytes could be obtained by leaving the animals in the gassing chamber for longer periods, and it seems probable that if the blood counts had been continued for several subsequent months a reduction of the erythrocytes would have been noticed eventually, corresponding to the anemia which often follows exposure to carbon monoxid in man.

In connection with the experiments of Nasmith and Harrison three points, brought out by recent observations, should be mentioned.

1. The observations were made during my personal experience with chronic carbon monoxid poisoning, during which I had the opportunity of studying the effects on four persons including myself without knowing the cause of the symptoms at first. I had abnormally high leucocyte counts (21,000), although there was no evidence of any infectious conditions. My patient, who was by far the most seriously affected, did not show leucocytosis, but her erythrocytes rose to 5,000,000, a fact which seemed inexplicable considering her debilitated condition; the unusual finding was verified by three independent counts. Of the two other persons, a friend and her husband who did not live at my house but who being neighbors spent a good deal of time with us, one, the husband, showed no sign of leucocytosis, whereas the other had fairly high leucocyte counts, up to 17,000, in the absence of any evidence of bacterial infection. It was discovered later that the furnace in the house of these neighbors was just as defective as the furnace in my house. (Figs. 37-41).

2. The investigations of Walterhöfer (1921) proved that the leucocytosis produced by injection of epinephrin is not due to any unequal distribution of the cells in the body, but to an actual increase in numbers. The leucocytosis produced by exposure to carbon monoxid would, therefore, seem to be connected with an initial stimulation of the adrenal medulla, whereas the secondary symptoms, muscular weakness, low blood sugar values and transient bronzing suggest a subsequent condition of temporary exhaustion of the whole gland. It is further of interest in this connection that experiments on four rabbits, fifteen dogs and four men (two of whom were in perfect health while the two others suffered from rhinitis, tonsillitis and bronchitis) at the University of Wisconsin by Leake (1922) proved that marked leucocytosis is produced by the injection of morphin (sulphate), and that according to Rogoff, "The effect of morphine in depleting the store of epinephrin from the adrenals has been confirmed by us" (Stewart and Rogoff, 1916 and 1918).

3. According to my observations patients suffering from carcinoma appear to have a tendency towards leucocyte counts of the low normal limit, 4000 to 6000, when the carcinoma is non-ulcerating and in the absence of intercurrent infection. This is particularly noticeable in the case of B, who had an amputation of the breast 1917 and who has remained free from recurrence (1922). During these years I had the opportunity of making numerous counts and chemical analyses on the blood of this patient (Figs. 33-36). For various reasons the observations on B were far less numerous between 1920 and 1922, than they had been from 1917 to 1920. The last diagram (Fig. 36) shows, however, that her highest leucocyte count was 6,700 and her lowest 4,600, representing the low normal limit, if 6,000-10,000 be accepted as the normal leucocyte range, as is done in the Mayo Clinic. Moreover, every one of the blood counts recorded in all of my diagrams was made before breakfast, at least twelve hours after the last intake of food, in order to exclude any influence of the post-digestive period and to put the blood counts on exactly the same basis as the chemical analyses of the blood. The tendency to low leucocyte counts in B is especially remarkable because, for at least a year if not longer, the Gas range in her house has been somewhat defective; it is in vain that I have endeavored to obtain the removal of this dangerous article of furniture, which announces its presence by a very noticeable odor of illuminating gas; fortunately B is out of the house a good deal. The fact that B, notwithstanding her exposure to illuminating gas, has failed to show any sign of leucocytosis points, so it would seem, to a certain sluggishness in her mechanism for the control of the leucocytic reaction.

The leucocyte counts of Anderson (1921) on thirty cases of mammary cancer should be mentioned in this connection. Anderson endorses the opinion expressed by Hayem, that the occurrence of leucocytosis in a patient suffering from carcinoma indicates a bad prognosis, and she endeavors to show that her findings corroborate Hayem's conception. At first sight my findings in the case of B might seem to support this view; but there are several considerations which suggest a totally different conclusion. Although the greatest credit should be given to Anderson for the careful, painstaking way in which her investigations were conducted, her deductions seem open to question for the following reasons. First: her observations only extend over a period of "from six to eighteen months", which is far too short a time to furnish conclusive evidence with regard to the fate of cancer patients, when they survive; eight of the thirty patients died within this period. Second: the counts were made "in the early afternoon, just before tea" that is, presumably less than six hours after the midday meal, when the influence of the postdigestive period cannot be excluded; in chemical analyses of the blood the influence of the postdigestive period is always given careful consideration, but it has received too little attention in the interpretation of blood counts; yet the work of Mauriac and Cabonat (1921), two French medical officers, who were in perfect health and who made blood counts on themselves at fifteen minute intervals for several consecutive days, shows that there is a marked increase of the leucocytes in the after-noon from 2 p.m. to 9 p.m., as that is during the postdigestive period, for the officers were on greatly reduced rations in a camp far removed from the firing-line, where they led a "peaceful existence", having little to do, and they carefully avoided physical fatigue during their investigation. (The findings of Mauriac and Cabonat will be discussed in detail in Chapter XII). Third: the "highest leucocyte figure obtained in the thirty cases was 14,400 (Case 25); the two other counts which Anderson obtained on this patient after operation on November 6, 1919, gave figures of 7,800 and 9,800 respectively, and the last available data on this patient "Stiffness in arm only complaint, October 15, 1920" shows a fairly satisfactory condition. As a contrast to these findings the leucocyte counts of another patient (Case 12) are interesting; this patient was operated on May 12, 1919, her leucocyte count on that date was 6,600, and May 20 it was 8,800, although she had "marked ulceration after operation" and she died October 13, 1919. A leucocyte count of only 8,000 in the presence of marked ulceration does not seem indicative of an active leucocytic reaction.

4. It is admitted that the leucocytic reaction is one of the great defensive reactions of the body. It is known that different types of bacterial infection call forth different degrees of leucocytosis, but that in pneumonia, for example, the patient who develops a hyperleucocytosis generally recovers, whereas the patient whose leucocyte count does not rise (other clinical symptoms being of the same severity) is very apt to die. If leucocytosis is a physiologic reaction in digestion and a defensive reaction against danger to the organism as it is in bacterial invasion, there is no reason for considering the leucocytosis produced by inhalation of carbon monoxid other than a defensive measure (Nasmith and Harrison, McCombs and others). The work of Walterhöfer, Leake and Stewart and Rogoff shows that the adrenals are instrumental in producing the leucocytic reaction. A lack of leucocytic reaction suggests a lack of response, a congenital inferiority, or a condition of exhaustion on the part of the adrenal mechanism. A reduction of adrenal efficiency in carcinoma is not only suggested by low leucocyte counts, but also by the evidence of mismanagement of cholesterol metabolism in cancer to which I have called attention repeatedly (Chap. VII); the adrenal glands, and probably the adrenal cortex in particular, appear to be among the chief administrators of cholesterol metabolism. In double-adrenalectomized dogs (Fig. 45) the total lack of cholesterol split products was observed, which I also found in 56 per cent of a series of seventy patients suffering from carcinoma; dogs deprived of their livers (Fig. 46) do not show any reduction of the cholesterol split products in their blood. In patients responding to radium treatment, or whose condition improved beyond expectation (Chap. IX,) the cholesterol split products (Bloor II) were found to increase, while the "pure" cholesterol (Bloor I) dropped simultaneously.

The sum total of the foregoing considerations and the evidence which they present suggest that noxious agents, which tend to impair the function of the adrenal glands must be capable of furthering the development of pathologic conditions in which manifestations of inadequate adrenal function can be observed. It is obvious that congenitally inferior or accidentally damaged adrenals will be taxed more severely by injurious agents than functionally strong and perfect glands.

If the inhalation of carbon monoxid taxes the adrenals, as it appears to do by producing an initial increase of the activity and finally a condition of more or less marked exhaustion of the glands; if a feeble leucocytic reaction and anomalies of cholesterol metabolism are indicative of inadequate adrenal activity; if feeble leucocytic reactions and cholesterol anomalies are often found in carcinoma, and if the heredity factor plays a part in the development of cancer, as is more than probable, then frequent and prolonged exposure to the carbon monoxid content of combustion products must further the development of cancer in persons whose adrenals are functionally below par, whether through congenital inferiority or through other causes. The deduction seems logical; evidence supporting it is by no means lacking and its bearing on the cancer problem is obvious.

Summarized evidence of the relation of combustion products to the cancer problem

The injurious effect of the carbon monoxid content of combustion products on the body as a whole and especially on certain of the endocrine glands; the work of Ross demonstrating the stimulation of malignant growth by the derivatives of bitumous coal; the investigations of C. E. Green showing the effect of the retention of combustion products and of the sulphur content of the staple fuel on the incidence of cancer; the observations of R. H. Greene and Killian on the disturbances of sulphur metabolism in malignant disease; the increase of cancer with increasing distance from the equator; and the parallel increase of cancer and of combustion products throughout the world, are facts which constitute a mass of corroborative evidence. This evidence furnishes much food for thought and assumes a startling significance when correlated with modern living conditions.

Hoffman (1921) has made the following statement: "The cancer problem is as baffling today, if not more so, than it has ever been. . . . The liability to cancerous affections is possibly 50 per cent greater than it was fifteen years ago. . . . General environment, topographic features and perhaps occupational pursuits may predispose to an excessive rate of cancer frequency. . . . Occupational cancers are a fact and not a theory. . . . Cancer is not only one of the most important causes of death, but the disease is increasing from year to year in practically all civilized countries. . . . This increase is real and not apparent".

Doubts concerning the actual increase of cancer have been expressed by Strong (1921) who bases his conclusions on the statistics of The Metropolitan Insurance Company (1911-1916) and of the Mutual Life Insurance Company (1915-1920). Strong points out that together with the factor of improved diagnosis, "A change in the age proportion of the population (such as change of residence of the younger members of a community) might be responsible for the entire apparent increase of cancer". He concludes, "We cannot now determine whether the cancer mortality is slightly increasing, practically stationary, or slightly decreasing, but we can be sure that it is not greatly increasing". And he says: "Lest what I have said be misinterpreted I would add that such conclusion does not at all lessen the seriousness of the cancer problem. It merely holds out hope that the terrible scourge will not increase without limit".

In this connection the following passage from an editorial in the Journal of the American Medical Association (1922, June 10), in which Strong's conclusions are discussed, should be quoted: "Insurance statistics are perhaps the most valuable we have in this country, for there is likely to be more care taken in giving the true cause of death when payment of insurance claims is involved. When, therefore, a competent statistician accustomed to study figures of facts without regard to tradition and unmoved by superficial guesswork applies rigid logic to premises which have been shorn of some of their obvious errors, he deserves a respectful hearing. . . ." This comment would seem to be at least as applicable to the data of Hoffman as to those of Strong; for Hoffman's statistical investigations cover a period of no less than thirty years and he has made cancer statistics an object of special research.

The relation of combustion products to the cancer problem is considered by Hoffman (1922) in his reference, "The investigations originated by Dr. C. E. Green of Edinburgh, continued by Dr. Georgine Luden of the Mayo Clinic, and brought near to a conclusion by Dr. Jerome Meyers, under the direction of Dr. Royal Copeland, Commissioner of Health of New York City". Hoffman adds: "I am not in a position to give expression to the final findings of these investigations further than to say that they are distinctly hopeful of practical results. In Rochester, Minnesota, Dr. Luden's investigations* would seem to show a decided effect of coal smoke as a causative factor in cancer occurrence. . . . I may, however, briefly refer to the New York investigations, the results of which have not yet been made public, but which were limited at my suggestion to Richmond Borough or Staten Island, where the conditions for such an investigation are practically ideal. That investigation covers the period from 1914-1920, including some 400 cancer deaths. The general indications are that areas subject to atmospheric irritants suffer a clearly traceable excess in the local cancer death rate over areas more favorably situated".

Preliminary investigations of the incidence of malignancy in Rochester, Minnesota, 1907-1918.

The topographic characteristics of Rochester, Minnesota, correspond in the main to those, which, according to Green's observations, increase the local incidence of malignant disease by the retention of combustion products. This

* Preliminary investigations including only citizens of Rochester who had been treated for malignant conditions at the Mayo Clinic 1907-1918; a copy of the find-

fact suggested that a study of the local incidence and distribution of cancer in Rochester might be of value either as a corroboration or as a contradiction of Green's findings. Several considerations made it seem advisable, however, to include in the analysis not the entire population of the city, but only residents of five years' standing in whom a definite diagnosis of malignancy had been made according to the records of the Mayo Clinic.

The population of Rochester, Minnesota, consists of a relatively small number of residents and a large number of transients. The majority of the transients are patients, many of them suffering from malignant conditions; they should, obviously, be excluded in an analysis of the local incidence of malignant disease. According to the census of 1910 the number of resident citizens was 7,884; in 1918 no definite data concerning the increase of the resident population were available, but the transient population was known to be close to 150,000. The census of 1920 revealed that the resident population had increased from 7,884 to 13,722 so that it had practically doubled in ten years.

Statistical data are usually based on the rate for each 100,000 population, because, "The fundamental principle of all statistical inquiries is the law of large numbers" (Hoffman). The application of this law becomes somewhat difficult, however, in dealing with a growing community, the rate of growth being unknown; as was the case of Rochester in 1918. My findings therefore are expressed in terms of the actual number of resident patients each year; but it should be borne in mind that the number of residents in Rochester increased twofold between 1910 and 1920.

The growth of a city does not, fortunately, alter the fundamental aspects of its topography. The number of its large buildings and their distribution may change, but if the town is situated in a valley, for example, the hills will continue to enclose the valley even though some of the hillsides be used for building purposes. Nor will climatic factors such as the direction of the pre-

ings was submitted to Dr. Hoffman, who suggested that the investigation should be extended by addition of all available data including death certificates.

vailing winds be changed by the city's growth in the absence of cataclysms like volcanic eruptions capable of transforming the character of the landscape. The erection of large buildings, however, in places where none stood before, is apt to produce a condition recalling the "air-pockets" known in aviation, which may further the occurrence of down-draughts and influence the elimination of combustion products in spite of the prevailing winds: it is for this reason that both the distribution of tall buildings and the prevailing winds deserve to be considered in an analysis of the relation of the local incidence of malignancy to local topographic characteristics.

The city of Rochester, Minnesota, is situated in a long fairly wide valley and surrounded by rolling country interspersed with stretches of flat land. The main portion of the town lies in a sort of cup or hollow formed by the surrounding hills; the valley is not entirely closed in, but is more or less open at its eastern and western ends. The river Zumbro, which forms several channels, roughly divides the town into an eastern and a western half. The northern portion of the city, containing the poorer districts, is the most thickly populated. The residential districts are growing in a south-westerly direction and slowly invading the hillsides. The roofline is very irregular, buildings of different sizes being unevenly distributed. Avenues of fine old trees are a characteristic feature of the city; many of the smaller houses are completely surrounded and hedged in by trees. (Figs. 47 and 48).

The prevailing winds, according to information given me by the weather bureau, are north and northwest in winter, spring and autumn, that is during the months when the greatest amount of fuel is used; but south and southeast winds are common during the summer months.

When I came to live in Rochester, 1914, the number of large buildings was relatively small, barely exceeding a dozen. These buildings, which might aptly be called the "chief smoke producers" were and still are located in or near the center of the town, at the bottom of the cup formed by hills; they include (going from West to East) the Court House, the Convent, the High School, the old Kahler Hotel of which the name has been changed to Damon, the Mayo Clinic, the Zumbro Hotel, the Public Library, the City Hall, the old City Powerhouse and a brewery. The railway stations of the North Western and the Chicago and Great Western, although small buildings, furnished a good deal of smoke and soot because of their roundhouses, freight trains and "switching" engines; the number of passenger trains was limited in 1914, but it increased during the following four years. St. Mary's Hospital, which lies at the extreme western end of the valley was already a large building; but the formation of the hills prevents the smoke of its private powerplant from reaching the city to any great extent.

Between 1914 and 1918 (September) no less than twenty large buildings were erected in Rochester; they have been marked in solid black on the city plan (Fig. 49) the older buildings being marked in outline only; their names, their location and the date of their completion is given in the following tabulation.

Large buildings erected in Rochester, Minnesota, 1914-1918.

1915..... 1. Colonial Hotel (afterwards hospital): First Avenue Southwest.
2. Northrup School: Second Avenue Northwest.
•3. Lincoln School: West Center Street.
1916..... 4. Stanley Hotel (afterwards hospital): Second Street and First Avenue Northwest.
5. Electric Power Plant: Second Avenue Northeast.
6. Masonic Temple: Second Street and First Avenue Southwest.
7. Addition to High School: Second Street and Second Avenue Southwest.
8. Security Hotel: North Broadway.
•9. Edison School: Seventh Street and Sixth Avenue Southwest.
10. Congregational Church: Second Street Southwest.
11. Case Auto Garage: Third Street Southwest.
12. Universalist Church: Third Street Southwest.
13. The Armory: North Broadway.
•14. Residence of Dr. W. J. Mayo: Fourth Street Southwest.
15. Lawler Theater: First Avenue Southwest.
16. Garden Theater: South Broadway.
17. Martin Hotel: Second Street Southwest.
1917.....•18. Hawthorne School: Seventh Street and Fourth Avenue Southeast.
19. Reiter Apartments: Second Street Southwest.
20. Norton House (hotel): Second Avenue Southeast.

It will be observed that nearly all of these buildings are situated within the one-half mile radius from the Postoffice (indicated by the inner circle on the city plan), with the exception of those marked (•); they also form a kind of barrier in the center of the town.

From the beginning of 1907 to September 1918 ninety residents of five years' standing were treated at the Mayo Clinic for malignant conditions. Of these ninety patients forty-five were men and forty-five were women; eighty-two were married and eight were single. A family history of malignant disease was obtained in seven only; but it is a well known fact that data concerning family histories are often misleading. Thus, one patient told the examining physician emphatically that "there never had been any cancer in her family"; the physician, who did not know the patient's family made a note of this statement in her history. Through information given me by an older member of the staff I discovered that the report of a microscopic diagnosis of carcinoma in the patient's father was on file in the records of the Clinic. Similar elements of error may have found their way into the histories of some of the other patients, although lack of evidence prevents their being traced and no blame can be attached to any one for their occurrence. The incident is noteworthy because it shows that the influence of the heredity factor in malignant disease may be merely hidden by negative data, and that reliable positive data are far more significant. Eighteen of the ninety resident patients had died in September 1918; necropsy was performed on seven. A histologic as well as a clinical diagnosis was made on sixty of the total number, the remaining thirty had only clinical diagnoses. Malignant epithelial neoplasia was found microscopically in fifty cases, benign or questionably malignant conditions being observed in nine; microscopic diagnosis of lymphosarcoma was made in one case only.*

The age incidence of the entire group of ninety cases is shown diagrammatically in Fig. 50; the age, in five-year groups, is given at the bottom of the chart; the number of cases in each age group is indicated by the height of

* Case A87659, male, married, aged fifty-four years, 1913.

the curve. There is a sharp rise in the curve (thirteen cases) corresponding to the age group of fifty to fifty-five and a second sharp rise (fourteen cases) corresponding to the age group of sixty-five to seventy years.

The relation of age and sex to the number of cases is given in Fig. 51. The curve representing the male patients (solid line) resembles that of the age incidence of the whole group; a sharp rise occurs between fifty and fifty-five and a similar rise between sixty and sixty-five years of age. The curve representing the female patients (dotted line) is quite different; the number of cases increases slowly but steadily in all of the age groups from twenty-five to forty-five, where the highest peak of the curve (six cases) is reached; there is a second rise between fifty and fifty-five, (corresponding to the first big rise in the men's curve) which is followed by a marked drop in the age group of fifty-five to sixty; the sharp rise which occurs in the curve of the male patients after sixty is absent in that of the females. My findings on the whole seem to agree with those in other statistics, inasmuch as they show that malignant disease in women tends to develop somewhat earlier in life than in men. However, the number of men (fourteen) in the age group with the highest incidence for men is much greater than the number of women (six) in the age group showing the highest incidence for women. These findings are interesting because the entire group of patients is composed of an equal number of men and women, but the total number, ninety, is too small for definite conclusions.

The number of resident patients each year during the eleven-year period of 1907-1918, according to their registration at the Mayo Clinic, is as follows: (it is shown diagrammatically in Fig, 52).

Year	Patients	Year	Patients
1907	2	1914	9
1910	1	1915	18
1911	1	1916	18
1912	2	1919	25
1913	2	1920	12 (six months only)

These figures point to a marked increase in the number of citizens of Rochester, Minnesota, who required treatment for malignant condition. Is the increase real or apparent? The growth of the population of Rochester fails to account for the increase in the number of resident patients. Inquiry had shown that the residents constituting the entire group had lived in the same district from five to fifteen years.* Even if the number of patients each year after 1913 be divided by two, in order to make allowance for the twofold increase of the resident population between 1910 and 1920, the increase in the number of resident patients is perceptible. The question therefore presents itself, whether any factors intimately connected with local conditions might furnish an explanation of the increase; the following considerations suggest an affirmative answer to this question.

1. Shortly after I came to live in Rochester, but long before I gave any thought to the possibility of a relation of combustion products to the cancer problem, I happened to observe that even in summer the smoke of Rochester generally hung like a black pall over the center of the city in the valley; but the smoke seldom came in the direction of my house, which is situated in the southwestern portion of the town, on the "edge of the cup" formed by the surrounding hills and which has been marked "L" on the city plan (Fig. 53). This observation was recalled when I read the book of C. E. Green and made me decide to study the local incidence of cancer in Rochester.

2. The topographic characteristics of Rochester, its location in a valley surrounded by hills, the distribution of its principal buildings and the direction of the prevailing winds, all tend to promote the retention of combustion products in the central portion of the city.

3. During the period in which the incidence of cancer among residents shows an increase, four factors undoubtedly contributed to increase the amount of combustion products in the city. These factors are: (a) the erection of

* I want to express my appreciation of the assistance given me by Miss Rott and Miss Murray of the Mayo Clinic in establishing the length of time during which the patients lived in given districts.

a considerable number of large, smoke-producing buildings and of many small or medium-sized private houses within four years; (b) the fact that the large buildings not only produced smoke, but also impeded its elimination by accentuating the irregularity of the roofline, by creating down-draughts and by forming a kind of barrier near the open side of the valley towards the east, thus hindering the elimination of combustion products by the prevailing northwesterly winds; (c) the marked increase of the number of automobiles, including those owned by citizens* and those belonging to transient visitors of the city, and the resulting increase of automobile exhaust gas, the combustion products of oil and of gasoline; and (d) the increasing use of soft, bituminous coal which began shortly after 1914, possibly as the result of economic conditions connected with the European War, and reached its height during America's participation in the War.

The sum total of these considerations and facts supports the idea that topographic and local conditions favored the production but reduced rather than augmented the elimination of combustion products in Rochester between 1914 and 1918.

In order to determine whether the retention of combustion products really had any influence on the incidence and on the local distribution of malignant disease in Rochester, the permanent residence of each one of the resident patients was marked on the city plan (Fig. 53); a dot(.) was used to indicate all the malignant cases, a crossed dot ($\dot{+}$) being used for those in which benign or questionably malignant conditions had been diagnosed and a query with a cross (?+) for which "rural delivery, postal district..." was the only available address; I am greatly indebted to the Postmaster for his assistance in helping me to locate the residences of the latter group.

A glance at the city plan (Fig. 53) shows that the area inhabited

* It proved impossible to determine the exact increase in the number of automobiles owned by citizens of Rochester; according to information furnished by the Secretary of State motor vehicles are registered for counties but not for individual cities; according to the Rochester Motor Garage the number of automobiles owned by citizens had increased at least five to sixfold during the four years.

by the largest number of citizens who were treated for malignant conditions coincides with the area in which the greatest amount of combustion products is retained on account of local topographic conditions, namely the center of the town, the "smoke area" at the bottom of the "cup" formed by the hills. The prevailing winds both in winter and in summer promote the accumulation of combustion products in this area; the elimination is likely to be hampered by the big buildings forming a kind of barrier towards the east.

Certain details which I was able to obtain concerning the living conditions of three of the ninety resident patients should be mentioned here. The house in which two of the patients, father and daughter, had lived since 1902 is situated in the southeastern portion of the town and overshadowed by big trees. Although it is not located, strictly speaking in the smoke area, the vicinity of the roundhouses of the Great Western railway causes it to be exposed to a considerable amount of combustion products; for the northwesterly winds carry at least a portion of the town smoke and all the smoke of "switching" engines in its direction and the surrounding trees prevent the smoke and soot from being dispersed and blown away. Six years after the family had moved into this house the father had an operation for epithelioma of the lip (microscopic diagnosis); six months later a papilloma of the larynx developed, but microscopic examination of the excised tissues only revealed a nonmalignant, "inflammatory" condition; according to the records of the Clinic, however, the gastric disturbances which caused the patient's death a few years later were indicative of carcinoma of the stomach, but no necropsy was performed. In 1917 the daughter, who had continued to live at the family residence, had an operation for cancer of the breast; histologic examination showed a rapidly growing, highly malignant type of cancer and glandular involvement; a recurrence within a year was expected by the surgeon, but the patient has been in good health for the last five years (1922); a detailed record of the variations in the chemical composition of her blood has been kept, small doses of thyroxin and dietary measures being used when the blood chemistry showed untoward changes (Figs. 33-36). Some observations on her blood chemistry have been discussed in connection with the relation of bacterial infections to the blood cholesterol (Chap. X); a complete analysis of the findings will be given in Chapter XII. Obviously, the fact that two members of a family living in a house that is markedly exposed to combustion products suffered from malignant conditions cannot be considered conclusive evidence of the effect of combustion products on the development of malignant disease; but the observations are of interest in connection with the findings of Green in England, Scotland, France, and the Orkney Islands and with my findings in Rochester, Minnesota.

In the third instance which came to my notice the patient lived, according to the address given in her history, in a house located on one of the highest hills, on the "edge of the cup" in the southwesterly portion of the town, that is, in a practically smoke-free district. Although there were many fine old trees around the house, it was by no means hedged in; as it was a mansion of considerable size the roof and the chimneys were high; the location as well as the direction of the prevailing winds prevented the town smoke from reaching this house to any appreciable extent. In an analysis concerned with the relation of combustion products to malignancy the occurrence of a case of malignant disease would naturally attract attention; albeit that many factors besides combustion products are likely to further the development of malignant conditions and that even strictly local factors, such as defective furnaces or imperfect gasfittings might furnish combustion products in ideally situated houses. It is interesting, however, that inquiry revealed that this patient spent very little time in the house which appeared to be her permanent residence; the occupation which she had chosen obliged her to live in the center of the town, the smoke area, in which the majority of the other patients resided. This observation, though it is by no means presented as conclusive evidence, shows the importance of details concerning the actual living conditions of the patients in an analysis of this kind; it may be impossible to obtain detailed information in many instances, but negative findings may also be merely the result of incomplete data.

Although the extent of my investigations is limited, the results tend to corroborate the findings of Green inasmuch as they point to a connection between topographic and local conditions which promote the retention of combustion products and the local incidence and distribution of malignant disease.

BIBLIOGRAPHY

1. Anderson, Ellen D.: The examination of the blood in cases of cancer of the breast in regard to operation and prognosis. Glasgow Med. Jour., 1921, xcv, 321-332; 402-420.

2. Benedict, S.R. and Rahe, A.H.: Studies in the influence of various factors in nutrition upon the growth of experimental tumors. I. Jour. Cancer Res., 1917, ii, 159-178.

3. Bierich, A.: Zur Energetik der Bildung maligner Tumore. Ztschr. f. Krebsch-forsch., 1921, xviii, 226-259.

4. Broders, A.C.: Squamous cell epithelioma of the lip. A study of five hundred and thirty-seven cases. Jour. Am. Med. Assn., 1920, lxxiv, 656-664.

5. Forbes, H.S.: A survey of carbon monoxid poisoning in American steel works, metal mines, and coal mines. Jour. Indust. Hyg., 1921, iii,11-15.

6. von Fürth, O.: The problems of phyriological and pathological chemistry of metabolism. Translated by A. J. Smith. Philadelphia, Lippincott, 1916, 682 pp.

7. Girault, A. and Richard A.: Intoxication par l'oxyde de carbone suivie de gangrene et de rétention recto-vesicale. Presse méd., 1922, xxx, 556-557.

8. Green, C.E.: The cancer problem. A statistical study. 3 ed. Edinburgh, Green and Co., 1914, 98 pp.

9. Greene, R.H.: Cancer, its nature, causes, diagnosis and treatment. New York, Dougherty, 1918, 172 pp.

10. Grove, W.R. and Vines, H.W.C.: The etiology and treatment of varicose ulcers. Brit. Med. Jour., 1921, ii, 687-689.

11. Haldane, J.S.: The action of carbonic oxide on man. Jour. Physiol., 1895, xviii, 430-462.

12. Haldane, J.S. and Smith, J.L.: The mass and oxygen capacity of the blood in man. Jour. Physiol., 1900, xxv, 331-343.

13. Hamilton, Alice: Women in the lead industries. Med. Woman's Jour., 1921, xxviii, 1-7.

14. Hamilton, Alice: A discussion of the etiology of so-called analine tumors of the bladder. Jour. Indust. Hyg., 1921, iii, 16-28.

15. Hamilton, Alice: The growing menace of benzene (benzol) poisoning in American industry. Jour. Am. Med. Assn., 1922, lxxviii, 627-632.

16. Harris, L.I.: Clinical types of occupational diseases. Jour. Am. Med. Assn., 1919, lxxiii, 880-886.

17. Henderson, Y.: Carbon monoxid poisoning. Jour. Am. Med. Assn., 1916, lxvii, 1-5; 580-583.

18. Henderson, Y.: How much gas can you breathe? Popular Sc. Month., 1920, xcvii, 19-22.

19. Henderson, Y. and Haggard, H.W.: The elimination of carbon monoxid from the blood after dangerous degrees of asphyxiation and a therapy for accelerating elimination. Jour. Pharmacol. and Exper. Therap., 1920, xvi, 11-20.

20. Henderson, Y., Haggard, H.W., Teague, M.C., Prince, A.L. and Wunderlich, Ruth M.: Physiologic effects of automobile exhaust gas and standards of ventilation for brief exposures. Jour. Indust. Hyg., 1921, iii, 79-92; 137-146.

21. Hoffman, F.L.: The mortality from cancer throughout the world. Newark, Prudential Press, 1915, 826 pp.

22. Hoffman, F.L.: Some new aspects of the problem of cancer control. Minnesota Med., 1921, iv, 124-132.

23. Hoffman, F.L.: The organisation of knowledge. Science, 1922, lv, 247-254.

24. Hoffman, F.L.: The cancer problem in the southern states. Jour. South Carolina Med. Assn., 1922, xviii, 51-57.

25. Kahn, M.: Sulphur metabolism in carcinoma. Jour. Cancer Res., 1917, ii, 379-391.

26. Leake, C.D.: Leukocytic reactions to morphin. Jour. Am. Med. Assn., 1922, lxxviii, 1687-1688.

27. Lewis, H.B.: The metabolism of sulfur. III. The relation between the cystine content of proteins and their efficiency in the maintenance of nitrogenous equilibrium in dogs. Jour. Biol. Chem., 1920, xlii, 289-296.

28. Luden, Georgine: The importance of visualising established scientific data with reference to the size of the body cells and their chemical supplies in the circulating blood. Endocrinology, 1921, v, 715-728.

29. Luden, Georgine: Chronic carbon monoxid poisoning; its immediate and subsequent manifestations. Modern Med., 1921, iii, 102-106; 167-170.

30. McAdie, A.: Atmospheric pollution. Science, 1922, lv, 596-597.

31. McCombs, R.S.: Clinical manifestations of illuminating gas poisoning. Am. Jour. Med. Sc., 1912, cxliv, 577-584.

32. McGurn, W.J.: Chronic gas poisoning - a brief but comprehensive report on fourteen cases. Interstate Med. Jour., 1917, xxiv, 479-487.

33. MacLeod, J.J.R.: Physiology and biochemistry in modern medicine. St. Louis, C. V. Mosby Company, 1920, 492 pp.

34. Matthews, A.P.: Physiologic chemistry. 2 ed. New York, Wm. Wood and Co., 1916, 1052 pp.

35. Mauriac, P. and Cabonat, P.: Contribution à l'étude des variations de la formule leucocytaire chez l'homme normal. Paris méd., 1921, xxxix, 407-408.

36. Nasmith, G.G. and Harrison, F.C.: Changes induced in the blood of rabbits by living in an atmosphere of water gas. Jour. Exper. Med., 1910, xii, 282-287.

37. Nassauer, M.: Ueber bösartige Blasengeschwülste bei Arbeitern der organisch-chemischen Grossendustrie. Frankfurt. Ztschr. f. Path., 1919, xxii, 353-399.

38. Nation's Health, 1922, iv, No. 8, 30 adv.

39. Opie, E.L.: The health aspect of smoke abatement. Acad. Med. Cleveland, 1922, iv, Bull. 20, 7-8.

40. Owens, J.S.: Quoted by McAdie.

41. Pearce, R.M.: Cancer of the pancreas and glycosuria. Am. Jour. Med. Sc., 1904, cxxviii, 478-483.

42. Phelps, C.C.: Stopping the chimney thief. Scient. Am., 1921, cxxiv, 100-117.

43. Pott: Quoted by Garrison, F.H.: An introduction to the history of medicine. 3 ed. Philadelphia, Saunders, 1921, 942 pp.

44. Robin, A. and Bournigault, A.: Le soufre dans le foie cancéreux. Bull. Acad. de méd., 1920, 3.s., lxxxiii, 178-196.

45. Rogoff, J.M.: On the liberation of epinephrin from the adrenal glands; with a discussion of some of the methods, employed in its investigation. Jour. Lab. and Clin. Med., 1917-1918, iii, 209-219.

46. Ross, C.H.: Induced cell reproduction and cancer. Philadelphia, Blakiston's, 1911, i, 423 pp.

47. Ross, C.H.: Further researches into cell reproduction. London, Murray, 1912, ii, 125 pp.

48. Ross, C.H.: Researches into induced cell reproduction and cancer. London, Murray, 1913, iii, 149 pp.

49. Ross, C.H.: Occupational cancer. Jour. Cancer Res., 1918, iii, 321-356.

50. Ross, C.H.: Absence of cancer in the arctic regions. Lancet, 1919, i, 528-529.

51. Sayers, R.R., Meriweather, F.V. and Yant, W.P.: Physiological effects of exposure to low concentrations of carbon monoxide. Public Health Reports, 1922, xxxvii, 1127-1142.

52. Sayers, R.R., Surgeon, P.A. and O'Brien, H.R.: The treatment of carbon monoxid poisoning. Nation's Health, 1922, iv, 163-164.

53. Stephansson, V.: My life with the Eskimo. New York, Macmillan, 1919.

54. Stewart, G.N. and Rogoff, J.M.: The influence of certain factors, especially emotional disturbances, on the epinephrin content of the adrenals. Jour. Exper. Med., 1916, xxiv, 709-738.

55. Strong, W.M.: Is cancer mortality increasing? Jour. Cancer Res., 1921, vi, 251-256.

56. Teague, M.C.: The determination of carbon monoxid in air contaminated with motor exhaust. Jour. Indust. and Engin. Chem., 1920, xii, 964-968.

57. Walterhöfer, G.: Die Veränderungen des weissen Blutbildes nach Adrenalininjektionen. Deutsch. Arch. f. klin. Med., 1921, cxxxv, 208-223.

58. Wilmer, W.H.: Effects of carbon monoxid upon the eye. Am. Jour. Ophthal., 1921, iv, 73-90.

59. Winters, S.R.: Gas-tubing tests. Scient. Am., 1920, cxxiii, 499.

60. Yarrow, T.J., Jr.: Chronic carbon monoxid poisoning with report of an illustrative case. New York Med. Jour., 1900, lxxi, 496.

Extended investigations on the incidence of malignancy in Rochester, Minnesota, 1908-1920.

It is at the suggestion of Dr. F. L. Hoffman, statistician and vicepresident of the Prudential Insurance Company of America, that I have extended my investigations on the relation of combustion products to the incidence of malignant disease in Rochester, Minnesota. The data for the years 1918, 1919, and 1920 and the death certificates for the entire period (1908 to 1920) have been included in the analysis; the year 1907 has been excluded, because the system of clinical records in use at the Mayo Clinic was adopted in 1908; moreover, only two patients were treated for malignant conditions in 1907.

My revised and extended statistics, like the preliminary investigations, deal exclusively with residents of Rochester, Minnesota, who had lived in the city at least five years. It has been pointed out that, according to the data of the United States Bureau of Census, the resident population increased from 7,884 in 1910 to 13,722 in 1920. The statistical material at my disposal will be considered under three headings: (1) death certificates for deaths from malignant disease, (2) case histories of resident patients treated for malignant conditions, and (3) case histories of resident patients treated for benign tumors at the Mayo Clinic from 1908 to 1920.

Benign tumors have been included in the analysis for the following reasons: (1) the biologic relation between benign and malignant growths is admitted and it is known that benign tumors are not infrequently the forerunners of malignancy; (2) if biochemical disturbances play an important part in the development of malignant tumors, biochemical disturbances of a lesser degree, and perhaps of a somewhat different character, are likely also to play a part in the development of benign tumors, and (3) it seems possible that outside factors capable of promoting the metabolic disturbances which further malignant growth might also further the development of disturbances leading to benign neoplasia.

The death certificates and the clinical histories will be treated as entirely separate entities, although with regard to malignancy they overlap to a certain extent. It was found, however, that to deal with the material in any other way would merely confuse the issues and also make a graphic presentation of the findings practically impossible; because, for example, some of the local residents mentioned in the death certificates were treated at the Mayo Clinic, while others suffering from inoperable, hopeless, malignant conditions remained under the care of their local physician; on the other hand several patients, all of them citizens for five years on whom a microscopic diagnosis of malignancy had been made at the Clinic, left Rochester to spend the last years of their life elsewhere, with the result that their demise is not on record in the death certificates. In several instances, also, the diagnosis given a death certificate seemed open to question, as in "cancer of the liver", unconfirmed by surgical intervention or by necropsy. Since it is the object of this investigation to prove or disprove the influence of local topographic conditions on the incidence of neoplasms, it seemed safer to base all deductions on definite clinical and largely microscopic findings; the death certificates have been added for the sake of completeness of the data and they have been analysed as far as it was possible to do so.

The material available for analysis consists of 110 death certificates, 144 case histories of malignant conditions and 146 case histories of benign tumors. The death certificates refer only to deaths from malignant disease; there are two deaths from sarcoma and 108 from carcinoma. In the clinical histories the malignant tumors are carcinomas (142) with the exception of the two sarcomas, mentioned in the death certificates, one of which occurred in a girl aged twelve (1919), the other in a man fifty-four (1919); in the group of benign tumors the following diagnoses are included: fibroma, adenofibroma, myoma, fibroids, cysts, dermoid cysts (benign), and lipomas.

No attempt will be made to give a detailed analysis of the histologic characteristics of the tumors, because the data needed for such a classification are not to be found in the death certificates and they are also lacking in those histories in which only a clinical diagnosis is given. An incomplete record of histologic details would be of little value in a study in which the influence of local topographic factors on neoplastic tendencies in general is the object of research. Histologic details, moreover, are apt to be a matter of controversy among pathologists; they may also be controlled to a greater extent than is generally admitted by the individual chemistry of the host in whom the tumor develops: witness the surprising lack of mitotic figures which has been observed in highly malignant, rapidly growing tumors.

In the analysis of the material at my command the following points will be considered and discussed: (1) the diagnosis; (2) the total number of deaths from malignant and from benign tumors which occurred in male and in married or single female citizens of Rochester, Minnesota, 1908 to 1920; (3) the annual number of deaths from malignant and from benign tumors during the twelve year period; (4) the organs and parts affected by neoplasia according to the death certificates, and according to the clinical histories during the year-groups 1908 to 1910, 1911 to 1915, and 1916 to 1920; (5) the influence of heredity and of injury on the development of malignant and of benign tumors as far as traceable in the clinical histories; (6) the relation of sex to the annual number of deaths from malignant and from benign tumors; (7) the relation of incidence, sex, and age in the group of malignant tumors; (8) the detailed analysis of the death certificates and of the clinical histories with reference to the year-groups, the incidence, the sex, and the ages; (9) topography and local factors in Rochester, and (10) the influence of topographic and local factors on the incidence of tumors in the city, with reference only to the data of the clinical histories.

<u>The diagnosis.</u> Only seven necropsies were performed on permanent residents, suffering from malignant conditions between 1908 and 1920, al-

though the number of death certificates issued for deaths from malignant disease was 110; one necropsy was performed in 1915, one in 1916, two in 1917 and three in 1918; details of interest concerning these necropsies are given in Table 7. It is especially noteworthy that the carcinoma of the pancreas (Case A169029, 1917), which was diagnosed clinically and confirmed by necropsy, had been preceded by diabetes in 1916, an unusual symptom in pancreatic carcinoma.
The fact that the patient, a man aged sixty-one, was engaged in the automobile business and thus considerably exposed to exhaust gas, recalls McGurn's observations on the rapid development of a severe type of diabetes in a healthy man during exposure to the carbon monoxid in soft coal smoke (see page 95, Case 13). The occurrence of carcinoma in the glands of the neck, the lungs and the prostate (Case A217398, 1918) is unusual also.

Table 7

Necropsies on citizens of Rochester, Minnesota suffering from malignant disease 1908-1920

Case	Year	Number	Sex	Age	Location of carcinoma	Details given in necropsy report
A125347	1915	1	F	70	Stomach	Extensive involvement.
A169291	1916	1	M	70	Gallbladder	Metastasis in liver and abdomen.
A182479	1917	2	M	44	Parotid gland	Cerebral abscess; otitis media.
A169029	1917		M	61	Pancreas	Metastases in liver and omentum; 1916, diabetes; in automobile trade.
A144231	1918	3	F	46	Gallbladder	1915, colloid goiter.
A225776	1918		M	53	Sigmoid	Liver involvement; peritonitis.
A217398	1918		M	66	Glands of neck	Metastases in lungs and prostate.

The clinical histories show that a microscopic diagnosis was made in 102 of 144 cases (71 per cent) of malignant tumors, and in eighty-eight of 146 (60.2 per cent) of benign tumors. The deductions drawn from the analysis have been based entirely on the evidence furnished by the clinical histories.

The total number of deaths from malignant and benign tumors in males and in married and single females during the entire period (1908 to 1920) are given in Table 8. It is of interest that there is a slight preponderance of males suffering from malignant conditions, as regards both mortality and morbidity. Another finding, which differs somewhat from the usual statistical data, is that more married than single female citizens of Rochester appear to have been afflicted with benign as well as with malignant tumors. Although the period covered by my analysis is twelve years, the total number of cases is small as compared with that given in the numerous statistics of different countries summarised by Hoffman, in all of which there is a preponderance of malignancy in males over females. It is possible that the law of large numbers alone suffices to explain my findings; unless the local topographic factors which will be discussed in connection with the topography of the city can be said to have affected the mortality and morbidity from cancer in the male population of the city. As a general rule, according to surgeons (Hoffmeyer, for example) malignant tumors of the uterus are more common in married women and benign uterine tumors more common in unmarried women. In my analysis according to organs and parts (Table 9) uterine tumors rank highest in number in the group of benign tumors: the fact that the total number of benign tumors in married women is twice as large as in single women in Rochester is interesting on that account; but no explanation of these findings can be suggested.

Table 8

Neoplastic disease in citizens of Rochester, Minnesota, 1908-1920.

	Number	Males	Females	Females married	Females single
1. Deaths from malignancy (Death certificates)	110	57	53	40	13
2. Malignant tumors (Case histories)	144	76	68	49	19
3. Benign tumors (Case histories)	146	33	113	76	37

The deaths annually from malignant and from benign tumors in citizens of Rochester is shown graphically in Figure 54 for the entire period of 1908 to 1920. The impression created by the diagram (Fig. 54) is that of a steady increase in the incidence of malignant and of benign tumors between 1908 and 1918, as shown by the clinical histories. The mortality, on the other hand, according to the death certificates, does not show as noticeable an increase. It is possible that the drop in the number of malignant and of benign tumors in 1919 and 1920 may be connected with the epidemics of influenza in the city, during these two years; the deaths, however, show no reduction in numbers. Is the increasing incidence of tumors to be accounted for merely by the increase of the resident population from 7,884 in 1910 to 13,772 in 1920? I have attempted to answer this question by dividing the entire period (1908 to 1920) into three groups of years; one group of three years (1908, 1909, and 1910), and two groups of five years each 1911 to 1915 and 1916 to 1920). The total number of deaths from malignant and from benign tumors for each of these "year-groups" is given in Table 10. The yearly average for each year-group as regards deaths, malignant, and benign tumors is established by dividing the number of years in each year-group into the number of cases in the year-group; the figures thus obtained for the last two year-groups (1911 to 1915, 1916 to 1920) are divided by two in order to eliminate the effect of the two-fold increase of the resident population; the result of arithmetical procedure is given

Table 9

Neoplastic disease in citizens of Rochester, Minnesota, 1908 to 1920,

according to year-groups, organs, and parts

Death certificates: Total number 110: M 57; F 53 (M: males; F: females)
Carcinoma 108: M 56; F 52
Sarcoma 2: M 1; F 1

	Stomach	Intestine	Miscellaneous*	Liver	Breast	Uterus	Face	Mouth	Sarcoma
1908 to 1910	8	2	-	2	2	2	2	-	-
1911 to 1915	15	7	3	5	3	1	4	3	1
1916 to 1920	12	11	11	5	5	4	1	3	1
1908 to 1920	35	20	14	12	10	7	7	6	2

	Stomach M	Stomach F	Intestine M	Intestine F	Miscellaneous* M	Miscellaneous* F	Liver M	Liver F	Breast F	Uterus F	Face M	Face F	Mouth M	Mouth F
1908 to 1910	6	2	2	-	-	-	1	2	2	2	2	-	-	-
1911 to 1915	7	8	3	4	2	1	3	2	3	1	3	1	3	-
1916 to 1920	8	4	5	6	5	6	3	2	5	4	-	1	3	-
	21	14	10	10	7	7	7	6	10	7	5	2	6	-

*This group contains carcinomas of the thyroid (1), lung (2), prostate (1), pancreas (1), "abdomen" (1), "melanotic tumor" (1), and "generalized cancer" (1).

Malignant tumors - Citizens treated at the Mayo Clinic - Total number 144: M 76; F 68. Carcinoma 142: M 75; F 67. Sarcoma 2: M 1; F 1.

	Face	Miscel-laneous*	Breast	Uterus	Stomach	Mouth	Intes-tine	Blad-der	Prostate	Liver
1908 to 1910	6	2	1	1	2	6	1	-	-	-
1911 to 1915	12	6	8	6	7	4	2	2	1	2
1916 to 1920	21	11	8	10	6	3	7	2	3	1
	39	19	17	17	15	13	10	4	4	3

	Face M	Face F	Miscel-laneous* M	Miscel-laneous* F	Breast F	Uterus F	Stomach M	Stomach F	Mouth M	Mouth F	Intes-tine M	Intes-tine F	Blad-der M	Blad-der F	Prostate M	Liver M	Liver F
1908 to 1910	4	2	1	1	1	1	1	1	6	-	-	1	-	-	-	-	-
1911 to 1915	9	3	4	2	8	6	2	5	3	-	-	2	-	2	1	1	1
1916 to 1920	15	6	6	5	8	10	6	-	4	-	3	4	2	-	3	1	-
	28	11	11	8	17	17	9	6	13	-	3	7	2	2	4	2	1

*This group contains carcinomas of the "neck" (4), "abdomen" (2), lung (2), pancreas (1), perineum (1), perineum and labia (1), parotid gland (1), gallbladder (1), scalp (1), scapula (1), hand (1), and "generalized cancer" (1).

Benign tumors - Citizens treated at the Mayo Clinic - Total number 146: M 33; F 113.
Types: adenofibromas, fibromas, myomas, primary hyperplasia, lipomas, and cysts.

	Uterus	Breast	Prostate	Miscellaneous*	Mouth	Face	Lipomas
1908 to 1910	9	1	3	2	-	-	4
1911 to 1915	13	5	2	4	1	-	3
1916 to 1920	51	13	8	5	3	7	10
	73	19	13	[illegible]	4	7	17

	Miscellaneous* M	Miscellaneous* F	Mouth M	Mouth F	Face M	Face F	Lipomas M	Lipomas F
	5	6	2	2	3	4	9	8

*This group contains benign tumors of the "pelvis" (2), "neck" (2), "back" (2), axilla (1), bladder (1), finger (1), labia (1), and axillary fold (1).

in Table 11, which shows that there is a noticeable increase in the number of malignant and of benign tumors in the citizens during the last five years (1916 to 1920), independent of the increase of the population, although the death rate has not changed.

Table 10.

Total number of deaths, of malignant and of benign tumors in citizens of Rochester.

Distribution in groups of years, or year-groups from 1908 to 1920.

	Number of years	Death certificates	Malignant tumors	Benign tumors
First year-group	3	17	19	19
Second year-group	5	43	52	30
Third year-group	5	50	73	97

Table 11.

Yearly averages of deaths from malignant and from benign tumors in Rochester, Minnesota: Figures corrected to eliminate the effect of increase on the resident population.

Yearly averages in	Death certificates	Malignant tumors	Benign tumors
First year-group 1908-1910	17÷3 or 5.6	19÷3 or 6.6	19÷3 or 6.6
Second year-group 1911-1915	$\frac{43 \div 5}{2}$ or 4.3	$\frac{52 \div 5}{2}$ or 5.2	$\frac{30 \div 5}{2}$ or 3.0
Third year-group 1916-1920	$\frac{50 \div 5}{2}$ or 5.0	$\frac{73 \div 5}{2}$ or 7.3	$\frac{97 \div 5}{2}$ or 9.7

Is the increase in the incidence of malignant and of benign tumors shown by the corrected figures (Table 11) during the last five-year period real or apparent only? It is not caused by the increase of the resident population of Rochester. It is actually somewhat greater than the figures indicate, because the increase of the resident population was less than two-fold (as has been assumed); since the population was 13,772 in 1920, and not 15,760 as would be the case if the population of 1910, 7,884, had really doubled. The facilities for medical diagnosis and treatment did not undergo radical changes between 1915 and 1920. It can hardly be assumed that the diagnoses recorded in the clinical histories were more accurate in 1918 than in 1915. There was, during the War, no lack in Rochester of "local" physicians (excluding the staff of the Mayo Clinic), which might have induced a greater number of citizens to come to the Clinic for treatment;* local physicians, moreover, have always been in the habit of referring patients with tumors to the Clinic. It is possible that a certain number of tumors were discovered accidentally in patients who came for treatment of the sequellae of influenza; but it is equally possible that tumors, which caused no symptoms as yet, remained undiscovered when the patient died of influenza. Few necropsies appear to have been performed on citizens of Rochester: there were only seven necropsies in 110 deaths from malignancy during thirteen years. The foregoing considerations suggest that the increasing incidence of neoplasms (60 to 70 per cent microscopic diagnosis) is more than apparent. Obvious changes in local conditions, on the other hand, all of which tended to promote the retention of combustion products, lend support to the conception that neoplastic tendencies in permanent residents of the city may have been considerably aggravated by the increase of combustion products in the atmosphere.

<u>The influence of heredity and injury.</u> Of the 144 permanent residents of Rochester treated for malignant conditions 1908 to 1920, sixteen gave definite histories of heredity and nine definite histories of injury. The relatives, in whom malignant conditions were reported to have occurred, included a paternal grandmother one, a mother one, brothers or sisters six, children three, and fathers five. Of the 146 resident patients with benign tumors twenty-four furnished information concerning malignant conditions in near relatives; the relatives included grandmothers three, fathers six, mothers six, brothers and sisters two, uncles or aunts four, and husbands two; the seven-weeks-old baby of a woman

* The lack of physicians during the War in many parts of Canada, caused numerous Canadian patients to come to Rochester for treatment.

aged thirty-seven with fibromyomas (microscopic diagnosis) had an angioma, the location of which is not given. A definite history of injury was furnished by a woman aged twenty-three with a fibroma of the breast: her chest had been hit severely by a slamming barn door six years previously. Details concerning the patients from whom a history of heredity or injury was obtained are given in Tables 5 and 6; no mention of heredity or of injury is made in the death certificates.

It has been pointed out previously how misleading negative data concerning heredity in malignant conditions are apt to be. The following incident, one among many in my records, shows how injuries may be completely forgotten by the patient even when the doctor makes every effort to obtain information on the subject. The patient in question was the wife of a physician, who takes an interest in cancer research; she lived in California, but had come to Rochester on account of a recurrent mammary carcinoma. She told the physician, who examined her, very definitely that she had "never met with either an accident or an injury", and the information was duly recorded in her history. A few days later she visited my laboratory and, in the course of conversation, described to me her experiences in Mexico, four years previously, during one of Villa's raids. The friends with whom she was staying had been obliged to flee in an automobile; they were going about fifty miles an hour when the pursuing rebels punctured the tires with rifle shots; the car turned a summersault which flung out the occupants including herself with considerable force. When I asked her in what position she had struck the ground, she replied: "Heavens, doctor, I could not tell you that, it knocked me out completely, but it did smash all my front teeth", and, by way of evidence, she forthwith extracted two "plates" for my inspection. As I happened to have read her history, I asked why she had not mentioned this accident, to which she answered: "For no other reason than that I never thought about it again till this minute". The character of the injury and the presumable force of the impact with the ground, which left the patient "black and blue all over" would seem to establish a connection between the accident and the malignant condition which developed four years later: it is obviously impossible to remove front teeth by a fall on the back. In this instance the circumstances attending the injury would seem exciting enough to insure remembrance, yet the patient failed to recall them during examination. It is as easy to surmise, as it is difficult to prove to what extent statistical data bearing on the relation of injury to malignant growth have been rendered worthless by the unintentional forgetfulness of the patient, which is often the direct result of nervousness or anxiety concerning the doctor's findings. If it were possible to obtain the necessary data in every instance a trauma of some sort would doubtless be found to have preceded every neoplastic manifestation, but it would also be found that trauma alone is as ineffective to produce malignant growth in the absence of biochemic disturbances as a spark is ineffective to cause an explosion in the absence of gunpowder, or its equivalent: explosions only take place when spark and gunpowder meet.

The influence of sex on the annual number of deaths from malignancy and on the incidence of malignant and of benign tumors is shown graphically in Figure 55. The slight preponderance of males over females with regard to deaths and malignant tumors, and the preponderance of females in the group of the benign tumors have been discussed and may be observed in the diagram.

The relation of incidence, sex and age in the group of malignant tumors is presented diagrammatically in Figure 56. It is interesting to note that the number of males in the age-groups in which the incidence of malignant disease is highest in males (the age-groups of fifty to fifty-five and of sixty-five to seventy) is relatively greater than the number of females in the age-groups in which the highest incidence of malignancy occurs in females (thirty-five to forty, fifty to fifty-five and seventy to seventy-five). The number of male citizens is also twice as large as that of female citizens of Rochester having malignant conditions which developed after the age of seventy-five years. The diagram (Fig. 56) indicates

Table 12

Data concerning heredity or injury in malignant conditions in citizens of Rochester, Minnesota, from 1908 to 1920

Year	Age and Sex	Type and location of lesion	Diagnosis	Injury years	Relatives
1908	41 M	Mixed tumor of parotid	Microscopic	8	Paternal grandmother had cancer
1908	81 F.	Cancer of the rectum	Microscopic		Two daughters had operations for "tumors"
1910	70 F.	Epithelioma of nose and cancer of cecum, appendix and hepatic flexure, died in 1912	Microscopic		Brother died of cancer of the stomach
1911	57 F.	Epithelioma of the hand	Clinical		Daughter had cancer of the sigmoid
1911	74 F.	Cancer of the breast, inoperable, died in 1911	Surgical	5	No data
1913	45 F.	Cancer of the breast, multiple fibromas in 1914; died in 1916	Microscopic		Sister had cancer of the breast
1914	65 F.	Cancer of the bladder, cervical polypi twenty-eight years ago, well in 1920	Microscopic		Husband died of cancer of the mouth in 1910, aged fifty-one years
1914	37 F.	Epithelioma of the forehead; injured the breast in 1912; tumor of the breast in 1913; chronic mastitis in 1919	Microscopic	1	No data
1914	88 F.	Epithelioma of the hand	Microscopic	1	No data
1915	65 F.	Cancer of the cervix, died in 1916	Microscopic		Father died of cancer of the stomach, aged seventy-six years
1915	70 M	Cancer of the cardia	Surgical		Brother died of cancer of the stomach
1915	67 M	Cancer of the lip	Microscopic	3	Sister had cancer of the breast
1916	37 F.	Cancer of the cervix	Microscopic		Father had cancer of the stomach and sister had cancer of the breast
1916	44 F.	Cancer of the breast (often "bumped" breast)	Microscopic	10 days	Sister died of cancer of the breast, aged forty-eight years
1917	53 F.	Epithelioma of the nose	Clinical		Brother had cancer
1917	38 F.	Cancer of the breast, well in 1922	Microscopic	10	Father died of cancer of the stomach(?); cancer of the larynx microscopically
1917	36 F.	Cancer of the sigmoid	Microscopic		Father had epithelioma of the hand in 1911
1918	53 F.	Cancer of the cervix	Microscopic		Mother died of cancer of the throat
1918	58 F.	Cancer of the cervix	Microscopic		One child died of diabetes

Table 12 continued.

1918	59 M	Cancer of the jaw; had leukoplakia in 1914, still has leukoplakia, but no recurrence of cancer in 1920	Microscopic		No data
1919	67 M	Cancer of the abdomen; broke several ribs; died in 1920	Microscopic	3 months	
1920	34 F*	Cancer of the breast; thrown against steering wheel in an automobile accident	Microscopic	2	
1920	50 M	Cancer of the esophagus	Clinical		Father died of diabetes

* Married
** Single

Table 19

Details concerning the heredity factor in benign tumors in citizens of Rochester, Minnesota, from 1908 to 1920

Year	Age and Sex	Type and location of lesion	Diagnosis	Relatives
1914	52 F*	Fibromyoma of the uterus	Microscopic	Father died of cancer of the stomach
1915	18 F**	Dermoid cyst, containing a lipoma	Microscopic	Maternal grandmother had cancer; grandfather had tuberculosis.
1915	39 F*	Uterine fibroids	Clinical	Mother had cancer
1915	39 F**	Fibrous ovarian cyst, myomas, cervical polyp; duodenal ulcer and appendicitis in 1919	Surgical	Sister had cancer of the uterus
1915	45 F*	Uterine myomas and polyp; tuberculous peritonitis, tubes removed in 1910	Microscopic	Mother had cancer of the breast; sister died of operation for "abdominal tumor"; much tuberculosis in the family
1916	65 F*	Papilloma of the back (insanity)	Clinical	Mother had cancer of the cervix (insanity)
1916	42 F*	Uterine fibroids	Clinical	Father died of cancer
1917	43 F*	"Tumor" of the breast	Clinical	Grandmother had cancer of the stomach
1917	34 F*	Fibro-adenoma of the breast	Microscopic	Grandmother had cancer and aunt died of cancer
1918	59 F*	Uterine fibroids	Clinical	Father died of cancer of the pancreas
1918	48 F*	Uterine adenomyomas, and multiple polypi	Microscopic	Father died of cancer (?); sister died of cancer of the breast
1918	44 F*	Uterine fibroids	Clinical	Husband died of cancer of the face and stomach; aged forty-three years
1918	37 F*	Uterine fibromyomas	Microscopic	Child, seven weeks, angioma (location not mentioned)
1919	38 F**	Uterine fibromyomas	Microscopic	Mother died of cancer
1919	55 F*	Uterine fibroids	Clinical	Husband died of cancer of the stomach
1919	49 F*	Uterine fibromyomas	Microscopic	Father died of cancer
1919	25 F*	Uterine fibroids	Clinical	Aunt died of cancer
1919	27 F**	Chronic mastitis	Microscopic	Mother had cancer
1919	47 M	Angioma of the tongue	Microscopic	Father died of cancer
1920	51 F*	Papillomas of the labia	Microscopic	Brother had Hodgkin's disease
1920	49 F*	Uterine fibroids	Clinical	Aunt had cancer
1920	45 F*	Lipoma of the neck	Clinical	Mother died of cancer of the breast
1920	38 F*	Uterine fibromyomas	Microscopic	Uncle had cancer of the stomach

* Married **Single

that malignant disease is apt to occur about ten years earlier in life in women than in men, which is in accordance with the usual findings; but it also shows that among citizens of Rochester more men than women become the victims of malignancy late in life, which seems an unusual occurrence, because general statistics tend to reveal a preponderance of females over males in the later decades of life, men being more likely than women to succumb to occupational and other accidents in the prime of life. The question presents itself whether local conditions in Rochester might account for the relatively high incidence of malignancy in older men. The following considerations are offered as a tentative explanation: The occupation of about one-third of the male citizens of five years' standing, in whom malignancy developed, is described in the clinical histories as "farming"; many of these were "retired farmers"; the remaining two-thirds were engaged in business of some sort which necessitated spending the greater portion of the day in the business district, that is, the center of the town. It has been pointed out previously that topographic factors promote the retention of combustion products in the center of the town. During the eight consecutive years in which I have lived in Rochester (1914 to 1922) I had the opportunity to observe that the majority of business men continued to carry on their respective lines of business in the same premises. If disturbances of the chemical balance in the body accompany advancing age; if biochemic factors play an important part in the development of malignant growth; and if exposure to combustion products alone tends to cause metabolic, that is biochemic disturbances, it would seem reasonable to assume that, when men of advancing years spend a great deal of their time in a district in which combustion products are particularly plentiful, opportunity for the development of malignancy may be called unusually favorable. The well known, high incidence of cancer among chimney sweeps shows the effect of combustion products and has been discussed indetail; it may not be a purely accidental finding that, among the seventy-six male citizens of Rochester, in whom malignant conditions developed, five at least were occupied in pursuits (such as "running the gas-plant for many years", "well-drilling" and the automobile business) which brought them into contact with considerable amounts of combustion products. The total numbers in my statistics are, of course, far too small for definite conclusions, but the observations may prove of value with regard to the etiology of malignant growth, if they can be confirmed by statistics on a large scale in which careful attention is given to the industrial pursuits as well as to the living conditions of the patients.

The detailed analysis of death certificates and clinical histories is presented in Figs. 57, 58, and 59. The relation of the incidence of neoplasia, with reference to numbers, sex and age, to the distribution of the cases in the year-groups 1908 to 1910, 1911 to 1915 and 1916 to 1920 is depicted graphically in these diagrams. A thick vertical line divides each diagram into a left and a right portion. The left side of the diagram represents the earlier decades of life, to forty-five years of age; the right side contains the later decades, from forty-five to seventy-five years and more. The male citizens are represented by solid black columns, the female citizens by superimposed "hatched" columns. The height of the entire column shows the total number of persons in a given age-group; each of the larger squares represents one person. For example, in Figure 57 (death certificates) the single black square in the year-group 1908 to 1910, under the age-group thirty to thirty-five years represents one male citizen, while the "hatched"square in the next year-group stands for one female citizen; in all of the three diagrams (Figs. 57, 58, and 59) the findings are depicted in the same way. In Figure 57 the columns representing males and females older than seventy-five had to be drawn side by side, because lack of space made it impossible to superimpose the columns.

Two observations of interest are brought out by the diagrammatic presentation of the statistical data. First, the height of the columns shows a tendency to increase from year-group to year-group, which is best seen by letting the eye travel from the top to the bottom of the diagrams. Second, the columns appear to "migrate" from the right to the left side of the diagrams, and this "migration" towards the left is particularly noticeable when the entries for the year-groups are compared. For example, there are no entries (Fig. 57) in the two first year-groups up to the age of thirty years whereas two entries are found in the year-group 1916 to 1920 in the earlier decades. The increasing height of the columns suggests an increase in numbers, while the "migration" of the columns towards the left indicates an earlier development of neoplastic conditions. The "hatched" columns of the females appear to lead, like pioneers, in this migration towards the left side of the diagrams, but the same tendency can also be observed in the solid black columns representing the males. The increase in numbers, as has been pointed out (page 127), cannot be attributed solely to the increase of the resident population, and the development of neoplastic tendencies at an earlier age would seem wholly independent of any increase in the population. It would seem logical to assume, however, that earlier manifestations of neoplasia might be influenced to a considerable extent by factors connected with local conditions and capable of furthering neoplastic tendencies. The factor of a more accurate diagnosis may be eliminated in Rochester and the activities of the American Society for the Control of Cancer, founded in 1913, were greatly handicapped by the War. They were resumed on a larger scale after 1918, that is at the time when the Rochester statistics show a slight decline in the number of cases, which may possibly be connected with the epidemics of influenza (page 157). Is there any evidence showing that local conditions, tending to promote the development of neoplastic tendencies, were present on a larger scale in Rochester during the years 1916 to 1920, than they had been in previous years? The following considerations suggest such a possibility.

<u>The influence of topography and of local factors.</u> The topographic features of Rochester, its location in a hollow or cup, between hills and local factors such as the irregularity of the roof line, the prevalence of north-

westerly winds in winter, spring, and autumn, and the distribution of the large buildings, have been discussed in detail (pages 107; 112). It has been pointed out that all of these factors coöperated to further the retention of combustion products especially in the central portions of the city. Such changes as occurred in the city between 1916 and 1920 tended to enhance rather than to diminish the effects of local and topographic conditions. To the number of large buildings erected between 1914 and 1918, twenty in all, no less than thirteen were added between 1918 and 1920; a description of these buildings is given in Table 14 and their location is shown on the city plan, Figure 60. It will be observed that the "barrier" of large buildings, mentioned in my preliminary investigations, increased in length and in breadth by the addition of the new buildings, the elimination of combustion products by the northwesterly winds being rendered somewhat more difficult. The irregularity of the roof line was further accentuated, as may be seen in Figures 61a and 61b, and the resulting production of down-draughts and "air-pockets" between large and small buildings promoted the retention of smoke, soot and other combustion products.

Table 14

Large buildings erected in Rochester, Minnesota, 1918 to 1920.

Year	Name
1918	1. The Worrell Hospital....215-219 Third Street, S.W.
	2. The Knowlton Store Building....Broadway and Second Street, S.W.
1919	3. The Coöperative Store....Broadway and Fourth Street, S.E.
	4. The College Apartments....Fourth Street, between Fourth and Fifth Avenues, S.W.
	5. The Lawler Store Building....229 First Avenue, S.W.
	6. The Curie Hospital....First Street, S.W.
	7. The Telephone Building....Second Avenue, between Third and Fourth Streets, S.W.
	8. The Edward Hotel....East Center Street.
	9. The Salvation Army Citadel....First Street, N.W.
1920	10. The Dental Building....Second Avenue, between Third and Fourth Streets, S.W.
	11. The Carlton Hotel....Center and First Avenue, N.W.
	12. The Arthur Hotel....Third Street and Second Avenue, S.W.
	13. The Campbell Hotel....Third Street and Second Avenue, S.W.

(The Kahler Hotel, the Alfred Hospital and the Holmes School were built in 1921; the new addition to St. Mary's Hospital and the addition to the Lincoln School were completed in 1922.)

The construction of numerous smaller, private houses, the continued use of soft coal, the ever-increasing number of motor vehicles and the quality of the gasoline used for automobiles, all combined to increase the amount of combustion products in the atmosphere. The effects of the increasing use of motor trucks burning the so-called bensol-mixture will be appreciated when the pungent, highly unpleasant odor of passing auto-trucks is recalled in connection with Hamilton's warning about the growing menace of bensol poisoning in the American industries (pages 69 and 70). The paving of a great many streets in Rochester during the last years furnished opportunity for greater amounts of exhaust gas to be dispersed in parts of the city, that used to be practically free from them.

While the erection of large buildings and the increasing number of paved streets are undoubtedly indications of the growth and the prosperity of a city, it cannot be denied that such aggrandisement is linked inseparably with an increased pollution of the atmosphere. Interesting observations published in the Scientific American (1921) show that even under the best possible conditions of fuel utilisation every 100 tons of coal furnish no less than thirty-five tons of useless combustion products in the form of soot and smoke. According to a rough estimate, for which I am indebted to the courtesy of the local coal merchants, 60,000 tons of coal have been used yearly on an average during the past few years. The combustion products resulting from the burning of this coal alone would amount to no less than about 20,000 tons (in round figures) or approximately 400 tons a week. In order to visualise the significance of these figures it should be remembered that 400 tons of some material like sand when piled up together will equal a large building in size. An estimate of the United States Geological Survey shows that the damage to property from combustion products alone amounts yearly to the sum of fifty million dollars in the United States; the damage to health caused by these

products may be approximated from the foregoing data. Opie, professor of pathology at Washington University, St. Louis, has recently published an interesting survey of "The health aspect of smoke abatement" and the fact that the American Society of Mechanical Engineers has appointed a commission composed of O. P. Hood, chief mechanical engineer of the United States Bureau of Mines, H. Kreisinger, P. J. Dougherty, L. R. Stowe, E. L. Millard, and Osborn Monnett to frame a standard smoke ordinance for all cities in the country, is a fact which speaks for itself.
It has been noticed recently in Paris that the famous shade-trees along the boulevards are showing signs of disease and that many of them are dying; an investigation by experts proved that the exhaust gas of the automobiles is responsible for the condition of the trees and as a result the municipal council of Paris has enforced drastic regulations with heavy fines for all "smoking" motor vehicles.

Certain details concerning local conditions in Rochester and some observations which I made personally are of interest because of their bearing on the increase of combustion products in the city. If it be recalled that the exhaust gas of automobiles contains from 4 to 12 per cent of carbon monoxid, or from 400 to 1200 parts in 10,000 of air, a casual observation published in one of the local papers becomes significant. The representative of the paper reports with pride that within thirty-five minutes (8.25 to 9 p.m.) no less than 200 automobiles and eighteen horse-drawn vehicles had been counted at the intersection of Fourth Street and Third Avenue, S.W., a location which is by no means characterized by the heaviest traffic. The majority of automobiles emit clouds of exhaust gas, partly as the result of the grade of gasoline now in use and partly through the carelessness of the owners with regard to the "setting" of the carburetor and the cleanliness of the engine; a phenomenon which may be observed as conveniently on warm summer evenings as on cold winter days, and of which the bearing on public health may be deduced by recalling the effects of exhaust on the shade trees in Paris.

I have mentioned (page 111) that during the first years of my stay in Rochester the smoke of the city which hung like a pall over the center of the valley did not reach my house even in summer with prevailing east or southeast winds. Of late years it has been a common occurrence to find the table on the screened porch covered with soot. My house is situated at the intersection of Third Street and Seventh Avenue, S.W., almost on the top of a hill; it faces north and has been marked "L" on the city plan (Fig. 60). Few automobiles used to pass because Seventh Avenue and Third Street have been paved only comparatively recently; Seventh Avenue has a steep grade and Third Street goes up a very steep hill immediately after the intersection. The steep grades now seem to have a particular fascination for motor drivers, presumably as they furnish an opportunity for testing the pulling power of the cars. In the wake of the automobiles and trucks, which are making (or endeavoring to make) the two grades, trails of exhaust gas may be seen at any time of day; and I have had ample opportunity to observe, watch in hand, that the bluish exhaust, on fairly windstill, but by no means windless days, remains hanging in the air no less than full five minutes; at the end of that time the exhaust gas having risen to a height of some twenty or thirty feet appeared to rebound from the wall of trees on the opposite side of Seventh Avenue and then pervaded the whole garden (an area of about an acre) with its distinctly offensive odor. Fourth Street is separated from the house by a distance of about four to five hundred yards; yet it is by no means rare in summer, with prevailing winds, for the exhaust of motor vehicles on Fourth Street to find its way into our bedrooms on the second floor, in amounts sufficient to permit distinguishing between the odor of automobile exhaust and the pungent, characteristic smell of the bensol mixture used in trucks. My study is on the ground floor of the house; its windows face Third Street and Seventh Avenue. Notwithstanding the fact that the garden is about thirty feet above the level of Third Street and that the house is separated from both thoroughfares by a distance of sixty to a hundred feet, the concentration of exhaust gas in the study is strong enough at times to even enable me to detect the odor, although the lack of keenness of my olfactory organ causes my friends to refer to it unkindly as an "odor-proof pathologist's nose". It need not be emphasised that under given conditions I have had plenty of opportunity to study in detail the minor symptoms of carbon monoxid poisoning, such as the peculiar numbness of face and feet, mentioned by Sayers and myself as well as the characteristic scalp headaches, the transient nausea and the general lassitude which inhalation of carbon monoxid are known to produce.

The foregoing details are given as an illustration of the extent to which combustion products invade our dwellings, even when they are particularly favorably situated. The observations have been recorded and checked with the greatest care, because they seem to deserve as much consideration as any phenomenon studied in the laboratory; they may be duplicated by any one who cares to take the trouble of keeping records on the subject for a period of from three to eight years. The amounts and the concentration of combustion products in those parts of the city in which the traffic is greatest or in which topographic and local factors favor their retention, may be deduced.

<u>The bearing of local factors on the incidence of tumors.</u> In my preliminary investigations the residences of the citizens who suffered from malignant conditions were marked on the city plan in order to determine whether or not local and topographic conditions had any influence on the local incidence of tumors. The same procedure has been adopted in my extended investigations and the results are shown in Figure 61. For the sake of convenience the two main thoroughfares, Broadway which runs from north to south, and Center Street running from east to west, have been made to stand out by a color wash on the city plan; the inner circle represents the distance of half a mile and the outer circle the distance of a mile from the post office, in the center of the town. The residences of patients with malignant tumors are indicated by a dot (.), those of patients with benign tumors

by a cross (+). For reasons which have been discussed (page 121) only the data of the clinical histories have been represented. The patients whose only available address was "rural delivery" are designated by the symbols of dots and crosses with an "R" followed by a Roman figure, approximately in the area of the rural, postal district. It may be mentioned that the highest number of cases appears to have occurred in the rural district R. II, south of the inner circle, where the country is somewhat more hilly, many of the farms being located in the folds of the hills.

With regard to the main portion of the city, the findings corroborate those of the preliminary investigation: the greatest number of cases is found to occur in the district located at the bottom of the cup formed by the hills, although, as has been pointed out this is not the most densely populated area. The fact that the district is inhabited chiefly by "fairly well-to-do" citizens recalls the observations made in Edinburgh concerning the relation of the house-rent to the incidence of malignancy. It is also true, however, that in this district the topographic formation, the winds which prevail during the seasons when the greatest amounts of fuel are used, and local factors such as the barrier of large buildings of which I have spoken, coöperate most effectively to further the retention of combustion products.

A closer examination of the city plan (Fig. 61) reveals several facts of considerable interest: (1) The cases of neoplasia appear to be distributed in groups or clusters, and this applies to the area in which the highest incidence is found as well as to the more favorably located districts. (2) As a rule the cases which are grouped represent both malignant and benign tumors, but at times one type of tumor predominates; thus, a group composed of six malignant tumors and one benign growth may be seer in the central district, just below the "School House" which has been outlined in Figure 61, whereas a group of five benign growths and one malignant tumor occurs in the southeastern portion of the city, between the inner and the outer circle, and a third group composed of eight benign growths and one malignant tumor is found on the inner circle on the west side; these groups have been encircled with a broken line to make them stand out. (3) It is noteworthy that in the portion of Broadway which is north of the railway lines, in the most densely populated part of the city, both malignant and benign cases should be found chiefly on either side of the street, only a few scattered cases occurring in the remainder of the district.

The following tentative explanation of findings shown in Figure 61 seems admissible, but the explanation offered should not be regarded in the light of a definite conclusion, and certain local characteristics of Rochester must be borne in mind. Although the city plan appears to be divided in city blocks, these divisions do not represent rows of houses with adjoining walls, but they represent "lots" occupied by single houses, which are separated by small or large gardens. The occurrence of cases of neoplasia in groups with intervening free spaces suggests therefore, that conditions favoring the development of neoplasia may have obtained in the small areas in which the groups of tumors are found. If the retention of combustion products favors the development of tumors, strictly local factors, such as the entrance of the smoke of a low chimney into the rooms of a taller neighboring building, slight defects in a gas-main shared by neighboring houses and so forth, may have helped in the formation of these groups. If biochemical disturbances promote the development of tumors, it seems reasonable to assume that severe biochemical disturbances produced by exposure to combustion products in a person with little resistance might lead to the development of a malignant growth, whereas biochemical disturbances of a lesser degree produced in a person with a more stable chemical balance might further merely the development of a benign tumor. The occurrence of progressively increasing neoplastic tendencies has been discussed in connection with the observations of Recamier and Celey (Part I, page). It is known that benign tumors may become malignant and the family history of malignant disease in near relatives of patients with benign tumors (Table 13) points to an intimate connection between benign and malignant growth. The double row of tumor cases found along the northern part of Broadway in Rochester may be connected with the fact that Broadway is the main thoroughfare for automobiles from the surrounding country; the inhabitants of houses lining the street are likely to be exposed to greater amounts of exhaust gas than the inhabitants of side streets.

I have suggested elsewhere that the carbon monoxid content of combustion products is a more potent factor in economic, social and domestic problems than has been realized. Carbon monoxid produces severe disturbances in the organism; recent observations show "the slowness with which these disturbances develop and the long delay before they right themselves" (Girault and Richard)*; the gas is also known to cause mental depression in some persons, but great irritability in others. It may be more than a coincidence that the greatest strike in the history of the United States has been staged by workers, miners and railway-maintenance men, whose exposure to combustion products needs no comment. According to statistics compiled before 1912, miners seemed to be singularly free from malignant disease; whether miners have remained thus immune after the introduction of modern mining methods remains for modern statistics to reveal.

The limited scope of my investigations in Rochester, Minnesota, has made it possible for me to consider many seemingly trivial details; such details may not prove to be available in researches on a larger scale, yet they may not be worthless. The evidence presented concerning a relation between neoplastic tendencies and combustion products is not offered as conclusive, but it may safely be regarded as an incentive to further research, and combustion products and malignant disease are to be found side by side throughout the world.

* "Ce que nous devons noter dans cette sorte d'intoxication, et l'observation que nous rapportons en est un seul exemple, c'est la lenteur d'eclosion dans les accidents et d'autre part la lenteur de reparation indiquant par la meme que les troubles de circulation et de nutrition des tissues se repercutent longtemps dans l'organisme dans l'anoxie un peu prolongee."

Chapter XXI

THE INTERRELATIONS OF BLOOD CONSTITUENTS AND FACTORS THAT INFLUENCE THEM

The idea commends itself as logical, that serial determinations made for several years on as many blood constituents as possible might throw some light on the interrelation of the constituents of the blood, reveal certain factors which influence the composition of the blood and perhaps also furnish clues concerning the biochemical disturbances which promote the lawless proliferation of cells. This idea became the basis of my work, when I began to study the blood cholesterol in 1915.

Many studies on the conditions of the blood in diseases such as anemias, leukemias, nephritis and diabetes had already been published, but data on the interrelation of blood constituents seemed scanty at that time. The majority of the investigators appeared to have taken an interest either in the blood picture, including erythrocytes, leucocytes, hemoglobin and differential counts, or in a few of the chemical components of the blood, such as the nonprotein nitrogen and the uric acid (Myers and Fine), the blood fats (Bloor, Windaus) or the blood sugar and the acetone bodies (Benedict and Lewis, v. Noorden, Allen, Joslin and many others). As a rule the investigations had consisted, so it seemed, either of single determinations on a number of patients, or at the best of a short series covering but a few months; I was soon to discover to what extent a formidable factor, the force of circumstances, accounted for the apparent brevity of these investigations.

Biochemistry, moreover, was barely out of its infancy in 1915; its popularity as a medical science was by no means great. Hawk's "Practical physiologic chemistry" was available and had already appeared in several editions, the first of which was printed in 1909; the works of Matthews, Bunge, v. Furth, Welch, Abderhalden and many others were to be had; Myers and Fine's "Chemical composition of the blood in health and disease" appeared in 1915; but the system of blood analysis of Folin and Wu was not made public until 1919.

Promising and commendable as prolonged investigations of the interrelation of blood constituents appeared to be in theory, in practice they proved to present even greater difficulties than I had counted on. Many of the difficulties were technical, but others were of an entirely different character; a few of them might be mentioned. Patients, naturally, desire to escape medical supervision and especially blood tests involving "pricks", as soon as they possibly can. The majority of the patients whose blood I could obtain did not live in Rochester; prolonging their stay, meant adding to their expenses. It did not seem justifiable to add to the discomfort of hospitalized patients, recovering from operations, by subjecting them to tests which might or might not yeild useful information, but unless patients are hospitalized it is practically impossible to obtain data concerning their diet and other factors. Attempts to induce ambulatory patients to keep records about themselves, ended, with rare exceptions, in a woeful fiasco.

The advantages and disadvantages of experiments on animals remained to be considered. Small animals, like rabbits and guinea pigs, do not survive too frequent bleeding. Dogs and cats are subject to spontaneous malignant tumors and useless, therefore, if the influence of changes in the composition of the blood produced experimentally was to be studied in connection with malignant growth. Goats were chosen in the end, for the following reasons: They are singularly free from neoplastic tendencies (Part II, page 10); their blood picture closely resembles that of human beings as I have shown; and there is no danger of killing the animals by taking samples of their blood repeatedly. Although definite changes in the blood picture and in the cholesterol content of the blood of goats were obtained under experimental conditions, 60,61 the goat's habit of chewing the cud made it impossible to study the effects of digestion. Unfortunately too, goats, like all experimental animals, are unable to voice their complaints. Yet the subjective feelings of a patient often furnish as much valuable information as objective findings.

The only plan which seemed to offer a solution to the problem of gathering data on the interrelation of blood constituents was to assume, myself, the role of experimental animal; in addition some of my friends might be induced to give their blood in a good cause. This plan was adopted, the results are shown in the diagrams (Figs. 23 to 44) and a synopsis of the material used in the investigation is given in Table 1 (page 19).

The experimental conditions furnished by using my own blood and that of friends willing to coöperate were by no means ideal. It was to be expected that the interpretation of the findings would be complicated by many factors beyond my control. However, the time of experimentation was unlimited, at least as far as I was concerned; subjective observations might be recorded for future reference; the influence of digestion could be eliminated at will and the effect of special diets or of therapeutic measures could be studied under strictly controlled conditions. On the whole, therefore, the investigation would not be much more severely handicapped than the majority of biologic observations on higher animals, in which intercurrent infections, for example, may also blur the picture. True, it remained a "make-shift", but at any rate the best available under given conditions.

At first, because of "mechanical" difficulties in a very general sense, only the relation of the blood cholesterol to the blood picture was studied. For the main object of my work, the connection between blood cholesterol and malignancy could not be lost sight of. Sources of technical errors and many side-issues had to be followed up. The influence of the blood cholesterol of many factors, such as the diet, intercurrent infections, malignancy, radiotherapy, hemorrhage and ulceration had to be investigated; the findings connected with these subjects have already been discussed (Chapters VII to X). My one helper, although willing and conscientious, was untrained; her training was part of the work; the work itself was of the type which does not proceed rapidly, and the days, unfortunately cannot be lengthened at will.

The progress made in gathering data on the interrelation of blood constituents was exasperatingly slow. The findings seemed to be contradictory in many instances; but it appeared reasonable to hope that an explanation of the apparent contradictions would be discovered when more data had been accumulated. In the meantime several interesting observations had been made. The value of parallel determinations with Bloor's two methods had apparently been established; the clues furnished by the lack of cholesterol split products in malignancy and their increase during conditions accompanied by an activation of metabolism (fever, ulceration, radiotherapy) have already been considered (Chapters VII to X). Data had also been collected on the influence of the "lymphoid defence" in malignant conditions (page 9, 69 Part II). It is interesting in this connection to note the correlation between certain data obtained in wholly independent investigations.

The importance of the lymphocytes in malignant disease has been emphasized by Murphy and Morton (1915), Stevens (1916), Luden (1917), Millet and Mueller (1918), and Vaughan (1919). Murphy and his collaborators have published a mass of evidence on the subject in their "Studies on lymphoid activity". Nakahara and Murphy (1921) in the tenth report of their "Studies on X-ray effects" call attention to the high degree of resistance to cancer transplants found in mice, in which "an increase of the number of lymphocytes" is accompanied by "a marked dilatation of the vessels in the suprarenals". Ordway and Knudson, in Barker's Endocrinology and Metabolism (1922) summarise our knowledge on the subject as follows: "It may be briefly stated that the lymphocytes are apparently stimulated to both relative and absolute increase by small doses and reduced in numbers by large doses of x-rays; and that the spleen and the lymphnodes undergo profound changes by destruction of cellular elements as the result of exposure to x-rays and radium".*

According to the findings of Grafe, of Murphy, Means and Aub, and of Edsall the pathologic, high leukocyte counts of myelogenous and lymphatic

* The significance of the lymphocytes and of the spleen in immunity to cancer has been questioned by Sittenfield and by Bullock and Rohdenburgh.

leukemia are accompanied by an abnormally high rate of basal metabolism; in the patient of Murphy, Means and Aub, a case of lymphatic leukemia, the rate was 44 per cent above normal. The improvement of the patients under radiotherapy coincided with a reduction in the number of lymphoid cells and a drop in the basal metabolic rate. The tendency to lymphocytosis and the increased rates of basal metabolism in hyperthyroidism (exophthalmic goiter) require no comment. These findings suggest some connection between the lymphoid cells and the rate of basal metabolism.

According to the observations of Kokkiji "a significant rise in basal metabolism as well as increased elimination of total nitrogen and uric acid" occurred in a normal person and in a patient suffering from chronic arthritis, after exposure to radium. Musser and Edsall noticed that clinical improvement in leukemias went hand in hand with an increase in the elimination of nitrogen, uric acid, purin bases and phosphorus pentoxid, and Mohr reported that in some patients with leukemia the elimination of uric acid continued to be high even in the presence of leukopenia. The questions which involuntarily present themselves in view of these findings, are: How did the lymphocytes behave in the cases studied by Kokkiji? What changes occurred in the rate of basal metabolism when the uric acid values of the blood remained unchanged as in the cases of myelogenous leukemia studied by Martin and Denis? Similar questions obtrude themselves with regard to the patients suffering from carcinoma studied by Killian and Kast; persistently high uric acid values in the blood seemed to indicate a bad prognosis; what was the metabolic rate of these patients, did they show any lymphocytic reaction? An answer to these questions would doubtless be of the greatest importance for the solution of the cancer problem. The study of the interrelation of blood constituents might help to find the answer, but the difficulties connected with this study are enormous; they can be expected to be solved only by organized coöperative efforts.

My observations on the relation of the lymphoid defense to cholesterol disintegration under radiotherapy gave apparently consistent and encourag-

ing results; patients whose lymphoid defence increased hand in hand with the amount of cholesterol split products in their blood seemed to do well, whereas those who failed to show a lymphocytic reaction and in whose blood the amount of cholesterol split products remained small, did not appear to derive much benefit from the treatment. It did not prove possible, however, to study simultaneously the blood reactions and the metabolic rate of these patients for the following reasons: Our metabolism laboratory was working to the limit of its capacity in determining the basal metabolic rate of patients with hyperthyroidism, for whom the chances in operative procedures were thus estimated; for patients with goiters both the rate of basal metabolism and operation were matters of vital importance; for patients suffering from malignant conditions the determination of the basal metabolic rate was merely a matter of scientific interest, of possible but unproved practical value. Single determinations of the blood cholesterol values in patients with hyperthyroidism had shown that when the basal metabolic rate was high the Bloor I, or pure cholesterol values, tended to be low and the amounts of split cholesterol fairly large; but serial tests on four patients with myxedema proved, on the other hand, that the rate of basal metabolism was not the only factor which influenced the rate of cholesterol disintegration. Although in myxedema the Bloor I values were high before administration of thyroxin, there was no lack of cholesterol split products, such as occurred in 56 per cent of the patients suffering from malignant
64
conditions. To discover which negligent organ might be responsible for the inadequate disintegration of cholesterol in malignancy seemed to be of paramount importance; this quest in my mind assumed the unscientific definition of "finding the lazy beggar", but many years were to pass before a clue pointing to any one of the organs became available.

It is somewhat surprising that those investigators who referred to my work in their papers have mentioned the reduction of the blood cholesterol following radium treatment, but have entirely omitted to mention the accompanying changes in the amount of cholesterol split products. The latter observation is by far the more important, as I have pointed out, because it shows that the absence of cholesterol split products in malignancy is connected with some kind of mismanagement of cholesterol metabolism, which appears to be corrected by radiotherapy, and which at present can only be revealed by parallel determinations with Bloor's two methods.

Henning, in 1922, in his work on the lipoids of the blood in tuberculosis, is the first, and as far as I could ascertain the only investigator, who has made use of parallel determinations with Bloor's two methods, to which he refers as the "saponification" method (Bloor I) and the "nonsaponification" method (Bloor II). According to his findings the saponified cholesterol values in tuberculosis are "uniformly low" and he considers the "unsaponified" cholesterol "normal". His findings correspond in the main to my earlier observations; the values which he reports are those to be expected in a disease like tuberculosis, characterized by chronic inflammatory processes, but his unsaponified cholesterol values are far above normal and similar to those found in all conditions accompanied by an activation of the chemical reactions in the body. In his determinations the difference between the saponified and the unsaponified cholesterol (or as I call it the difference between the Bloor I and Bloor II values), ranges from 80 to 100 mg. and more for each 100 c.c. According to my observations this difference ranges in normal persons, under normal conditions during the postdigestive period (that is, twelve to sixteen hours after the last intake of food) only from 17 to 34 mg. There are some slight personal variations, but I have found during my study of nearly 3,000 individual blood samples that the normal range of the difference (17 to 34 mg.) may increase three or fourfold during the process of digestion, in the presence of intercurrent infections, "colds" for example, and ulcerating wounds, following hemorrhages and after radiotherapy in patients capable of responding to the treatment; in malignancy before radiotherapy, on the other hand, the blood samples taken during the postdigestive period of roughly one-half of the patients show a complete lack of difference between the saponified and the unsaponified cholesterol values, which reveals the total absence of cholesterol split products in the blood. It is noteworthy that one of Henning's patients (Case 8), who was "discharged from the hospital as improved", had a normal difference (16 mg.) between his saponified and unsaponified cholesterol values. It is greatly to be regretted, however, that with the exception of one man on whom two tests were made to "check the method", only single determinations were made by Henning on his twenty-one patients.

The difference in value between the saponified cholesterol (Bloor I) and the unsaponified cholesterol (Bloor II) is ascribed by Henning to the presence in the blood of "a relatively large amount of an unknown substance which is closely related to cholesterol". In 1917 I pointed out that the extensive researches of Lifschütz, on which my own observations were based,[62] prove conclusively that this "unknown substance" consists in reality of several cholesterol derivatives including oxycholesterol, but chiefly oxidised cholic acid and presumably other, intermediate products of cholesterol disintegration. I am using the term "disintegration" advisedly and in preference to "oxidation", because oxidation in the strictly chemical sense of the word may not be the only factor responsible for the occurrence of these bodies in the blood, and it seemed safer in 1917 to refer to them as changed cholesterol or cholesterol split products.

The recent investigations of Lifschütz (1921) show that after the removal of the cholesterol from the blood both oxycholesterol and dioxycholesterol are included in the digitonin precipitate, but that "the material not precipitated with digitonin gives a strong cholesterol reaction and appears to contain three additional oxidation products of cholesterol". Therefore Henning's unknown substance would seem to be composed of at least three bodies and perhaps four (including oxidised cholic acid), all of which have claim to the title of cholesterol split products.

The work of de Niord, Schreiner and de Niord (1920) on the changes in the blood of patients suffering from cancer treated with roentgen-rays should be discussed in this connection. The blood constituents included in these investigations are: cholesterol, fatty acids, total fats, sodium chlorid, urea nitrogen, creatinin, blood sugar, diastatic ferment, and the relation of plasma to corpuscles; the blood samples were taken before exposure as well as one-half hour and twenty-four hours after exposure to the rays; forty-eight patients were studied. They found that the blood cholesterol, fatty acids and total fat values were generally high before exposure; an observation which corroborates my findings and recalls the investigations of Freund and Kaminer concerning the presence in cancer of abnormal products of fat metabolism. De Niord, Schreiner and de Niord state, however, that the changes which occurred in all of the blood constituents after exposure to the roentgen rays are too irregular and too inconsistent to warrant conclusions. There are several points which deserve to be considered with regard to this statement.

1. The method used for the determination of cholesterol by de Niord, Schreiner and de Niord is not mentioned definitely, but the bibliographic reference which is given points to Bloor's second, nonsaponification method as the only one employed. Since parallel determinations with Bloor's two methods alone seem capable of revealing the behavior of the blood cholesterol, as I have shown, the unsatisfactory character of the findings of de Niord, Schreiner and de Niord is easily explained.

2. It seems possible that the time allowed to elapse after exposure, one-half to twenty-four hours, was barely sufficient for definite changes in the composition of the blood to become established. Data on this point are still very scanty, but the consensus of opinion among radiologists appears to be that the effects of radiation take some time to develop. According to Quick of the Memorial Hospital in New York, "The inflammatory effects of radiation are not apparent

for several days"; the technic of radiation used at the Mayo Clinic is described by Bowing as follows: "X-ray treatment is repeated every three weeks until eight or ten treatments have been given; after a wait of three months it is determined whether further therapy is necessary". It goes without saying that the type and the location of the tumors determine the dosage and the course of the treatment in the individual case, but the foregoing quotations show clearly that the changes wrought by radiotherapy do not become manifest in a short time. It is obvious therefore, that serial determinations, covering several weeks, alone can be expected to increase our knowledge of the chemical reactions produced in the body by radiant energy.

3. It is known that the final oxidation products of cholesterol do not give the characteristic green color reaction; the gradual "fading" of cholesterol tests to a dirty yellow is familiar to all who have made the determinations. In samples treated with Bloor II, nonsaponification method[62] varying amounts of cholesterol split products occur. It seems possible that several factors, including the photoactive properties of radium and roentgen rays (since cholesterol is disintegrated by photoactive rays, according to Schulze and Winterstein) as well as the increased activity of various organs, may coöperate to reduce half-oxidized cholesterol to completely oxidized fragments, which no longer add to the color of the tests. The further disintegration of cholesterol split products is shown in Figure 6; the last but one entry in this diagram represents the blood cholesterol findings before the patient's last exposure to radium; she has a large amount of cholesterol split products which is in contrast to the lack of split cholesterol in the first entry; her condition had shown marked improvement; the last entry represents a test made only three hours after the last radium treatment and shows a reduction of the split cholesterol as well as of the values of the saponified (Bloor I) cholesterol. The diagram illustrates the value of the parallel determinations; the details of this case are discussed on page 11. These considerations

may help to explain the decrease, resulting from more complete oxidation, of the unsaponified, Bloor II cholesterol values which de Niord, Schreiner and de Niord observed in 31 per cent of their patients, and the increase, caused by partial oxidation which they found in 61 per cent.

4. There are two other factors which undoubtedly influenced the irregular and baffling findings reported by de Niord, Schreiner and de Niord, but which (as far as I could ascertain) do not seem to have been considered in radiotherapy. These factors are the influence of the rays on the organs which control the chemistry of the body, such as the liver and the glands of internal secretion; and the capacity for response to stimulation of different organs in different persons.*

The activation of the hemopoietic system by moderate amounts of radiation and the destruction of this system by excessive amounts have been studied and recognized (Ordway and Knudson). The histologic changes produced in the gonads by exposure to radium or roentgen rays are too well known to require comment. Radiotherapy has been employed for exophthalmic goiter (C. H. Mayo, Murray and others) and for the secondary hypopituitarism of certain cases of acromegalia (Beclere, Beck); the clinical improvement of the patients indicates the influence of the rays on those glands which are connected with the clinical symptoms; but the chemical changes associated with the improvement of the patients do not seem to have been studied.

It is inconceivable that the lymph glands, the spleen, the bone marrow and the gonads should "feel" the stimulus of the rays and that the liver, the adrenals and other organs should fail to do so. The metabolic changes connected with radiation, such as increased elimination of nitrogen, phosphates, uric acid and the transient appearance of cholin in the blood (Musser and Edsall, Ordway and Knudson) are usually attributed to the destruction of cells and their nuclei, al-

* Since the above was written a brilliant exposition of the chemical changes and the effect on different organs as well as the treatment following irradiation with roentgen ray has been published by Harat.

though the effect of the rays on the body enzymes has been taken into consideration (Neuberg). I have pointed out elsewhere (page 19 Part II) that the high blood cholesterol values in malignancy and the altered behavior of the blood cholesterol after radiation cannot be explained by cell destruction only; but that changes in the activities of the organs which regulate the blood chemistry must be assumed to play an important part in the readjustment of cholesterol metabolism when the patient responds to radiotherapy. The same considerations would seem to apply to the changes in the nitrogen, the phosphate and the uric acid metabolism; and possibly also to the decrease of the alkaline reserve following radiation, as reported by Dennis and Martin. It is noteworthy that the observations of de Niord, Schreiner and de Niord on the high uric acid values of the blood in carcinoma have been fully corroborated by Killian and Kast (Part I, page 126), who found that the prognosis was bad for patients in whose blood high uric acid values persisted. Of the thirty-six patients whose blood uric acid was determined by de Niord, Schreiner and de Niord, only two had normal values, fourteen had excessively high values, while four patients who died all showed high values, which increased after radiation in three of them but remained unchanged in the fourth.

The foregoing comments are not offered in any spirit of criticism, for no one can realise more fully than I the many difficulties associated with investigations of this type; they are offered in the hope that they may prove of some use in future investigations, because further studies concerning the influence of radiant energy on the organs which control the body chemistry are urgently needed.

The technical handicaps to which I have referred made it impossible for a long time to collect data on any other blood constituents but the cholesterol, the lymphoid defence, the leukocytes, the erythrocytes and the hemoglobin. In 1919 the aquisition of a second helper made it possible to include the blood catalase and the blood sugar as well as the blood cholesterol and the blood cytology in the study of the interrelation of blood constituents. Under given conditions the blood catalase determinations failed, however to yield much information; although interesting observations during experiments on animals have been reported by Myers and Killian. The catalase tests were discontinued after June, 1920.

The epidemics of influenza (1918-1920) furnished an opportunity to study the behavior of the blood cholesterol during bacterial infection and its bearing on the problems of immunity by means of our serial determinations; the sharp rises of the saponified (Bloor I) cholesterol at the onset of acute infection and during recurrences of influenza have been discussed in detail in connection with the work of Manfredi in Chapter X.

The detailed notes which I kept concerning myself as an experimental animal and concerning friends who gave me their blood, and to whom I want to express my thanks for their loyal coöperation, proved to be of the greatest value; for they helped to explain the riddle of the many symptoms produced by chronic carbon monoxid poisoning. The observations which I made and wrote down while in total ignorance of the cause of the variable symptoms proved to be fully corroborated by the data of other observers; as I found when I began to study the literature on carbon monoxid, after the defects in my furnace had been discovered and strongly positive Katyama tests (Matthews) had demonstrated the presence of carbon monoxid in my blood and that of my friends. In a recent editorial of the Presse médicale (1922), all the minor symptoms of chronic carbon monoxid poisoning to which I called attention in 1919 are discussed in detail. The editor's warning was inspired by the occurrence of eleven deaths in one day in Paris from carbon monoxid poisoning; he makes the following comment: "One would think that this treacherous gas takes a special delight in assuming an underhand character, which causes its misdoings to be blamed on other factors, for the disturbances which it causes are but too often attributed to other causes".*

The experience gathered during the weeks of the "carbon monoxid

* Recently further corroboration was found in the text-book of Lewin, "Die Kohlenoxydvergiftung" (1920) which was difficult to secure because of economic conditions in Germany.

episode" in my house proved to be useful in many respects. It called my attention to a factor which is not only of paramount importance in the study of the interrelation of blood constituents, but which may complicate the problem of correlating the findings to a most distressing extent. This factor is the relative efficiency, or capacity for response, of various endocrine organs in different individuals. It is a factor which does not seem to have received much consideration in connection with biochemical findings; for I have been unable to trace any reference to it in the discussions of clinical observations or experimental data. The clinical aspects of this factor have been summarised recently by Hoskins (1922) in the following words: "In cases of frank primary deficiency of some one endocrin organ the problem is relatively simple. But as it presents itself clinically the problem is very frequently complicated by the possibility of interrelations among various glands. A given cause may act simultaneously on several members of a related congeries of organs producing hypertrophy due to overfunction in each. But hypertrophy of one of a related pair may also be due to the vicarious assumption of the function of the other. This is the common interpretation of the pituitary hypertrophy which follows thyroidectomy. When one organ normally exercises a check on another, hypertrophy of the second may result from a depression of the activity of the first. If on the other hand, one organ normally stimulates the other, as the thyroid does the suprarenal, hypertrophy of the second may be due to overactivity of the first. In view of these different possibilities of interpretation to determine in case of any observed clinical phenomenon its actual cause is frequently difficult or impossible. . . . . From the data of the foregoing discussion it appears that research in the field of endocrin biology is beset with difficulties on all sides."

Hoskin's definition of the difficulties of researches in endocrin biology applies fully to the difficulty of the interpretation of biochemical findings. It will be readily granted, for example, that the chemical products resulting from the activities of a capable thyroid and inferior adrenals are likely to differ materially from those furnished by the activities of an inferior thyroid and capable suprarenals. To complicate matters still further, variations are known to occur in the activity of the same organ in the same person at different times; but we have as yet no means by which to gauge the zeal or the lack of zeal with which many of the organs may be attending to their respective duties. The bitter controversy between clinicians and physiologists on the subject of suprarenal insufficiency need only be recalled; clinical manifestations interpreted as evidence of reduced adrenal activity, such as asthenia and cardiac irregularities, were held up to ridicule because they could not be duplicated in animals which survived experimental damage of the adrenal glands (Sergent, Sajous, Steward and Cannon). The "white line" of Sergent was found to occur, for example, by Wright in 66 per cent of 100 young medical students although the men appeared to be in excellent health. Wright points out that "the white line is produced by local emptying of the capillaries due to the active contraction of some elements in their wall", and that there is no reason to assume that the phenomenon has any pathologic significance connected with the efficiency of the adrenals. Cohoe concludes his synopsis on hypoadrenia with the comment: "In conclusion it may be emphasized that most of the literature on 'hypoadrenia' betrays a profound ignorance (of modern physiology) on the part of the writers and a remarkably cacalier attitude towards the cannons of logic"; and he adds: "It is probably a safe forecast that a decade hence much less will be heard of clinical suprarenal deficiency".

It is somewhat difficult to understand why both the thyroid and the heart, for example, should be allowed the privelege of a "half-time" schedule, since it is admitted that there are mild as well as severe forms of myxedema and transitory as well as permanent forms of cardiac decompensation, and why the suprarenals alone should be assumed to be subject to an iron rule of "all or nothing". Such, however, is the impression created by the utterances found in many of the discussions on suprarenal activity.

The recent work of Scott (1922) on experimentally produced suprarenal insufficiency in cats seems likely to hasten the aforementioned prophecy of Cohoe to the resting place of unfulfilled prognostications. Scott studied the effects on the basal metabolic rate, the temperature and the general welfare of his animals of procedures calculated to reduce the activities of the adrenal glands. Thirty-five experiments, covering a period of over three months, were made on twenty-four cats. The methods used to lessen the functional capacity of the suprarenals were the following: (1) partial excision, which gave "entirely unsatisfactory" results, because the cats died in a short time when too great a portion of the glands had been removed and showed no ill effects when the resected portion was too little, whereas the margin of safety appeared to be very small; (2) bilateral ligation of nearly all the adrenal veins, which gave good results in some cases only, because the establishment of a collateral circulation proved to be the dominant factor, although it was impossible to control or to predict the influence of this factor, and (3) freezing of the glands with a fine ethyl chlorid spray, which gave the best results, as the amount of injury could be regulated. All the technical details and the carefully selected methods used for the controls cannot be considered here; they will be found in the original.

Scott's observations may be summarized as follows: When the injury to the suprarenals is not very severe, the animals live indefinitely and their metabolic rate remains unchanged. When the injury is sufficient, but nonfatal, a marked rise occurs in the rate of basal metabolism; the animals feel warm objectively, their appetites increase; but there may be periods of transient asthenia and marked depression, while at necropsy evidences of a restoration of adrenal function and of increased thyroid activity are to be found. When the injury is very severe the animals may survive for about a week, but the basal metabolic rate declines consistently, there is a progressive asthenia and far-reaching destruction of the suprarenals together with signs of depletion, and retrogressive changes in the thyroid are found at necropsy. It is of interest to recall in this connection that the average life of a cat is about seven years, that is, roughly one-tenth of the lifetime of a human being, so that one week for a cat is equivalent to ten weeks or three months for man. The rapidly fatal course of Addison's disease, in a few months and less in some cases, is well known (Lippmann, Motzfeldt, Cohoe and others).

The protocol given by Scott of one of his animals (Cat 18, Group II) is so interesting that I may be allowed to quote it in slightly abbreviated form. The cat was a three-quarter grown female. Determinations of the basal metabolic rate were begun in the middle of September, 1921, and bilateral ligation of the suprarenal vessels was done October 20. Two days later the cat "felt warm", was "active and eating well"; but by October 25 she was "very quiet, and not eating"; October 26 she seemed "very weak" and was "coughing occasionally". The appetite returned however. November 18, or about a month later, the cat began to lose weight and strength; the appetite was poor; she was given 25 mg. of potassium iodid by mouth. November 19 the cat was "very weak and listless, scarcely holding up her head"; she was then given "emulsion of alcoholic extract of residue of ox suprarenal cortex", by mouth from a pipette. A sudden transformation in her behavior followed. The notes on November 20 are: "Very active and alert this morning, remarkable appetite, eating 100 gm. of meat without intermission". No more suprarenal cortex was given, but the administration of potassium iodid was continued at intervals until December 30 when the cat was killed, having "gained in weight" and "improved in appearance".

The basal metabolic rate of this animal showed a sudden increase to 44 per cent above the preoperative average on the first and fifth days after ligation of the suprarenal veins and "the rate remained elevated for twenty-five days". But at the time when the cat began to show symptoms of asthenia and to lose appetite and weight (November 18) the basal metabolic rate had dropped to 20 per cent below the preoperative figures. After the administration of the single dose of adrenal cortex followed by continued administration of potassium iodide, when the cat was alert and eating greedily, the basal metabolic rate "rose continuously for three days to a point above the preoperative range; it then became subnormal for a week, after which it resumed the original level". At necropsy (December 30) the right suprarenal was found atrophied but the left gland had acquired a collateral circulation and its tissues presented the histologic picture associated with normal function; the thyroid on the other hand showed active hyperplasia of the epithelium and the colloid had disappeared from the acini.

In view of the foregoing findings, it seems reasonable to assume that the single small dose of adrenal cortex temporarily tided the animal over its worst period of depression, since it is known that the organism works with incredibly small amounts of its chemical constituents, and that the capability of response of the thyroid together with the development of a collateral circulation in the left suprarenal enabled the animal finally to recover its balance of health.

The importance of Scott's investigation is such that some of his findings in animals which developed a fatal suprarenal insufficiency should also be mentioned. Thus, "gastric ulcer was frequently observed in this series in confirmation of the observations of others"; similar results have been reported by Finzi, Mann and Durante, but it is especially interesting that Durante obtained only small, scattered, transient hemorrhages in the gastric mucosa when he damaged, by way of the lumbar route, the large, the medium and the small splanchnic nerves of the right suprarenal or the large and the small splanchnics of the left gland, whereas he produced typical permanent gastric ulcers and changes in the spleen as soon as the medium splanchnic nerve of the left suprarenal had been injured, whether alone or in conjunction with the other nerves. Scott found, moreover, that the "symptoms of disturbed gastro-intestinal function, most often manifest as diarrhea, were usually evident during the period of suprarenal insufficiency, most frequently observed at the time of maximal increase in basal metabolism". In two cats which survived a fatal insufficiency for more than a week "operative recovery was prompt, but a secondary profound weakness manifested itself about the fourth day, which was well in advance of the stage of marked reduction of food intake". Other observations of Scott's made in the severer types of suprarenal injury recall the well known manifestations of carbon monoxid poisoning, namely: "the heart action becomes irregular, the mucous membranes sometimes cyanotic and the animal goes into collapse on slight exertion". McCombs emphasizes the dangers of exercise and exposure to very cold air in cases of carbon monoxid poisoning; I have experienced the effects of going out into the cold after exposure to carbon monoxid and have pointed out the similarity of the symptoms of carbon monoxid intoxication to those attributed to suprarenal insufficiency.

The fluctuations in the welfare and in the basal metabolism of those among Scott's animals, which, like Cat 18, managed to recover from the injury to their adrenals through the assistance of their thyroids, and the comment of Murlin that, "Even under the most uniform conditions thus far applied, the basal metabolic rate has been found to vary from day to day and from hour to hour in the same individual, and even more in different individuals", should be borne in mind when an attempt is made to correlate biochemical findings. It is comforting to reflect, however, that the prolonged studies on themselves by Johanssen and Magnus Levy, for periods of seven months and two years respectively, revealed a certain constancy in the behavior of the basal metabolic rate in a given person, during long periods and in the absence of severe accidental disturbances. There is, consequently, some hope of discovering an interrelation between the changes in various blood constituents by serial determinations on the same person, under approximately uniform conditions for many months or years; whereas it is obvious that no such correlation can be expected to appear in single determinations made on different persons, no matter how large the number of single tests.

A detailed discussion of the difficulties, handicaps and problems connected with the study of the interrelation of blood constituents was unavoidable, before the observations made by serial tests on my own blood for seven years and on that of other persons for periods ranging from two months to five years, could be considered. The observations are not offered as conclusive evidence, which could not have been obtained under given conditions; they are presented in the hope that they may be of some use to other investigators, perhaps as a basis for further research.

The chief intercurrent factors which are likely to have influenced my findings and the work of others which contradicts, corroborates or explains them will be taken into consideration. For a sake of completeness clinical histories of A, B, C, D, and F, on whom long series of determinations could be made, are given; but it would be impossible to mention all the minor clinical observations on which notes were kept for a number of years, daily entries being made; the variable symptoms connected with the exposure of some of us to carbon monoxid alone would fill many pages and these symptoms have been described in detail elsewhere. 65

Since it is the object of this communication to call attention to the interrelation of certain blood constituents, to the clues which they seem to furnish concerning the activities of some of the endocrine glands, and to the need of biochemical investigation of the problems of malignant growth, the following points will be discussed:

1. The clinical histories connected with the diagrams (Figs. 23 to 44).

2. The relation of the total leukocyte counts to the blood cholesterol values.

3. The relation of the blood cholesterol and the blood sugar values.

4. The two aspects of the biochemical conception of malignancy.

All those who voluntarily gave their blood in the good cause will feel more than repaid if these studies should prove to be even of the slightest value in the battle against malignant disease, although I fully realise that the work is but fragmentary and far from complete.

Clinical histories connected with the diagrams (Figures 23 to 44)

A, the writer, an unmarried woman, native of the Netherlands, aged forty-seven, had croup and measles as a child, recurrent fever (Spirillum obermeieri) for five years between twenty and twenty-five years of age, and at the age of thirty-two septicemia with a temperature of 42°C (106 F) for a week, followed by complete recovery without sequellae; this septicemia was the result of a scratch on the hand contracted during the necropsy of a patient with puerpural sepsis. Since then A has not known a day's illness and remained immune during the epidemics of influenza (1918-1920), possibly as the result of injections of a prophylactic vaccine against influenza, although the vaccine did not produce immunity in every instance (Chapter X), and although a culture of Pfeiffer bacilli was obtained from her nasopharynx. During nine weeks' exposure to the odorless fumes of a defective central heating system, 1919, A exhibited the following symptoms of carbon monoxid poisoning: precordial pain, cardiac irregularities, numbness of face and feet, scalp headaches, transient muscular weakness especially in the legs, high leukocyte counts and a transient bronzing of the entire body, without, however, being incapacitated for work at any time. No lasting ill effects have been observed with the exception of a kind of hypersensitisation to carbon monoxid, which causes a transient return of most of the aforementioned symptoms on exposure to slight amounts of automobile exhaust, illuminating gas or chimney smoke. The phenomenon of hypersensitisation has been checked carefully for experimental purposes. The symptoms show a constant sequence, beginning with numbness of face and feet and ending in two or three days with a feeling of great lassitude and cold. It has so far been impossible to discover why certain symptoms vary in intensity on different occasions, but it has been noticed, for example, that at times severe precordial pains are associated with very little headache, while at other times the scalp headache dominates the picture, the other symptoms being present only in a minor degree, for no apparent reason. The symptoms develop when A, who has practically no sense of smell, is wholly unaware of the presence of any kind of gas, but the initial symptom, numbness of face and feet, has proved quite useful by calling attention to small, unsuspected gas leaks in the laboratory and to unknown defects in the house of friends on many occasions, when A's "diagnosis" has proved to be correct on investigation.

The paternal grandmother of A died, according to family reports, of a gastric cancer, 1841, but no necropsy was held; the paternal grandfather died of angina pectoris, 1872, at seventy-two years of age; the maternal grandmother succumbed to smallpox during an epidemic of this disease, after she had declined to be vaccinated; the maternal grandfather lived to be ninety-six and died of "old age".* The father of A died of Bright's disease at the age of forty-nine and the mother of an ectopian pregnancy at the age of thirty-six; A's only brother is alive and well.

B, an unmarried woman aged forty-two, native of the United States, had a Halsted operation for carcinoma of the breast in 1917; histologic examination revealed a highly malignant, rapidly growing type of tumor; there was some glandular involvement. After operation B was given only one roentgen-ray treatment of 20 ma. on the right and 20 ma. on the left side of the chest (October 22, 1917). Following exposure to the roentgen rays the amount of cholesterol split products, which had been satisfactory, decreased to such an extent that there was no split cholesterol in the blood (Fig. 39). This was regarded as an untoward sign and roentgen-ray treatment was discontinued. November 26, 1917 B received 1150 mg. hours of exposure to radium, followed December 3, 1917 by another exposure of 2700 mg. hours. The exposure to radium caused a marked and rapid increase of the cho-

* and in excellent health and very active to the last, although an inveterate smoker.

lesterol split products in the blood (Fig. 33). Since then B has not had any radiotherapy but her diet has been regulated according to requirements indicated by the cholesterol determinations and she has been given small amounts of thyroxin, 3 to 5 mg. in divided doses at intervals; the administration of thyroxin has been marked "T" on the diagrams. Although at the time of operation a recurrence was expected within a year and the patient was not expected to live longer than three years at the most, she has been free from recurrence and in excellent health to date (1922). The reaction of B to the injections of prophylactic vaccine against influenza have been discussed in Chapter X; she remained immune to the disease during all the epidemics of influenza although she came into close contact with several patients suffering from influenza. B could not give much information with regard to the diseases of childhood; she "supposed she had had them", but she recalled having measles when about thirty years of age and being very ill at the time. About four years before carcinoma developed in the left breast (June, 1917), she had shown a very marked increase in weight, up to 160 pounds, although her normal weight is 140 pounds (similar observations have been made by the writer in a number of other patients suffering from carcinoma); at that time B also developed a skin eruption which disappeared under treatment, and she suffered a good deal from "neuralgic" pains in various parts of her body. During the past year the presence in B's house of a gas cooking range the odor from which frequently noticeable has been looked on with concern by the writer; unfortunately the gas range cannot be eliminated on account of local conditions. The general trend of the blood curves is being watched therefore, with special care, as the biochemical findings, though still satisfactory, show a slight tendency in the wrong direction.

The father of B had an operation for cancer of the larynx and died of gastric disturbances which, according to the records of the Mayo Clinic, strongly suggested gastric carcinoma, but no necropsy was made. The mother of B died of an acute form of pneumonia; her numerous brothers and sisters are alive and well. One of B's married sisters had an operation for bilateral corpus luteum cysts and an appendectomy, 1910, and a posterior gastro-enterostomy for duodenal ulcer, 1919.

C, a married woman, native of the United States, aged thirty-seven, suffered a good deal from "sore throats" as a child. She had an appendectomy and unilateral ovariectomy about thirteen years ago and a cholecystectomy for chronic cholecystitis in 1915; no gallstones were found at operation, but the history of typical gallstone attacks, given by the patient, suggests that gallstones may have formed and been passed during previous years. C had a moderately severe attack of influenza in 1918. She has never had any children. Before her second marriage C lived in the house of A for five years and her consistently high hemoglobin values (80 to 85 per cent) were a matter of some surprise in connection with her general condition; she also complained frequently of scalp headaches, shortness of breath and pain in the calves of her legs. In view of the observations made during the nine weeks of carbon monoxid production in the house of A in 1919 ("the coal gas period"), it seems possible that the central heating system in A's house may have been somewhat defective for a much longer time than was definitely proved. During the "coal gas period" C and her husband were frequent visitors at A's house, but the symptoms which they developed, such as headaches, sleeplessness and lassitude were attributed to prevalence of influenza, although neither of them contracted the disease during the epidemic of 1919. Several months after the defects of the furnace in A's house had been discovered, several sources of carbon monoxid production were also found in the house of C and D; namely, first a corroded iron breaching (the pipe connecting furnace and flue), which, since rusty, corroded iron becomes porous, allowed the furnace fumes to escape into the house; second, the use of one chimney flue for two furnaces, (one furnace for hot water supply, the other belonging to the hot water heating system) which led to down draughts as soon as one fire burned with greater intensity than the other. It is noteworthy that the sleeplessness, headaches and nervous irritability of C and her husband completely vanished, and that domestic happiness was restored as soon as structural changes had been made in the heating system which provided a flue for each furnace and a new iron breaching. The reaction of C to the prophylactic vaccine against influenza in 1920 has been discussed in Chapter X; although C nursed her husband and came into contact with several other patients she remained immune.

The maternal grandfather of C died of tuberculosis at the age of fifty-eight; the maternal grandmother had "crippling rheumatism" for many years and died at the age of sixty; her paternal grandfather died of "dropsy" at sixty-eight, and her paternal grandmother, whose violent temper was feared by the family, died of "old age" at eighty years of age. The father and mother of C are both alive and in good health; it is feared that her only brother has incipient tuberculosis, but her three sisters are living and well.

D, the husband of C, a native of the United States, aged thirty-five years, had mumps and measles as a child and no other serious illness until the winter of 1915, when he began to suffer from repeated, severe attacks of tonsillitis. He developed "rheumatic fever" shortly after, but all his symptoms cleared up permanently following tonsillectomy in 1916. He was in the army during the War and received prophylactic injections against typhoid and paratyphoid fever in 1917 and against influenza and pneumonia in 1918. Although he was in one of the Southern training camps where the mortality from influenza-pneumonia was very high, and where he assisted in caring for the patients, he remained in excellent health. At the end of October, 1919 when defects in the central heating system (hot water heating) of A's house began to be suspected, D accompanied A into the fume-laden basement to investigate the matter; the effect on his blood sugar is shown in Figure 40 and will be discussed in connection with the influence of exposure to carbon monoxid on the composition of the blood. Although D received another prophylactic injection against influenza in January, 1920, he had a moderately severe attack of influenza toward the end of February. The total leukocyte counts of D show a persistent tendency towards the lowest normal range; they are frequently below 5,000 and sometimes lower than 4,000, even when D is perfectly well. It seems possible that D's double exposure to furnace fumes, in A's basement and in his own house where he attended to the firing of a defective furnace, together with his low leukocyte counts helped to break down his resistance to influenza in 1920, as he had proved to be immune during the far more severe epidemic in the army in 1918; for his wife (C), whose leukocyte counts were of a much higher range (Figs. 37 and 38) and who was exposed to smaller amounts of carbon monoxid did not contract the disease at this time.

The family history of D is negative as far as tuberculosis and malignancy are concerned. His maternal grandfather died of "a stroke" at the age of sixty-eight; his maternal grandmother, at the age of eighty-eight, is in full possession of all her faculties. His paternal grandparents were among the pioneers who settled the State of Minnesota; D knows little about them except that they are reported to have died of "old age", well advanced in years. His father, mother and twin brother are alive and well.

F, an unmarried woman aged thirty-five years, a native of Canada but of Irish descent, came to Rochester in 1919. In her case the interpretation of the biochemical findings is complicated by many factors. She had an acute attack of appendicitis with perforation of the appendix and peritonitis at the age of six, from which she recovered without operation after many months of illness. At intervals for about twenty years she had many attacks of peritoneal irritation, accompanied at times by rises of temperature up to 102° F., but these attacks were attributed to "nervous excitability", while she was at school. Finally at the age of twenty-seven an appendectomy was performed and evidence of the rupture of the appendix and its subsequent "walling off" were found at operation. The following data, obtained first in the course of conversation, but confirmed by careful inquiry, are of special interest. Between her twentieth and thirtieth years F was exposed four times to considerable amounts of carbon monoxid. The circumstances were as follows:

1. She lived for three years in a house which was lighted and heated with illuminating gas and in which the odor of illuminating gas was more or less noticeable most of the time.

2. She spent a summer in Scotland in a house situated next to the gas-plant, the odor of gas at times being such as to oblige the inhabitants of the house to keep the windows closed, and to prevent them from remaining in their garden.

3. She was a member of the choir of a church in which the hot air furnace was known to be in bad condition; all the members of the choir noticed that the fumes of this furnace caused them to be "rather short of breath"; and F had often wondered why she should have such a feeling of constriction in her chest when singing in the choir, though she was never troubled with lack of breath when singing elsewhere.

4. There was a hot air furnace in F's home, which often made the atmosphere rather oppressive, especially in the evening and it had been observed, before F came to Rochester, that her health generally broke down after she had been at home for any length of time, the fact being attributed to "the climate". It may be of interest to add that when I visited F's old home a short time ago I was able to remove portions of the mortar between the bricks of the furnace-flue with my finger nails; some of the pieces thus obtained show small blackened canals, which look as if they had been made with a dental drill and which furnish unquestionable evidence of the escape of the furnace fumes into the basement (Fig. 42a) since it is known that lime-mortar is disintegrated and rendered porous by the action of combustion products.*

* The use of lime-mortar for chimney flues has been prohibited in the Building Code of the National Board of Fire Underwriters in the United States (1915) on account of "fire hazard". It is obvious that fire hazard implies the escape of fumes. Lime mortar will be found, however, in many houses built prior to 1915 even in the United States; the house referred to is in Canada.

At the age of twenty-nine, while at her home, F developed a severe pyelitis; practically pure cultures of <u>Bacterium coli</u> were obtained from the urine, but all tests for tuberculosis by experiments on guinea pigs gave negative results. The pyelitis cleared up completely after Kelly's fixation operation had been done on the left kidney; and F's general health improved greatly; she gained twenty pounds and was able to do a great deal of work in connection with the home activities of the Red Cross during the War.

At the age of thirty, while in excellent health, she hurt her left breast by running against a stair-post in the dark; but she noticed no immediate effects. A year later a small, apparently cystic "lump" developed in the left breast together with a persistent cough. As her mother had had a benign tumor of the left breast which was removed by amputation, it was considered safer to excise the small cystic tumor. Operation revealed that F's breast was more seriously involved than had been apparent; an enucleation was done; the diagnosis of the pathologist was fibro-adenoma and he characterised the tissues as showing "a borderland condition".

F had numerous attacks of influenza at various times, and she succumbed to the prevalent epidemic of influenza-like "colds" shortly after she came to Rochester to work in the laboratories in August, 1919. During a visit at A's house she had a fainting spell, which at the time was ascribed to the effects of the influenza as cardiac disturbances were common during this epidemic; it is possible, however, in view of the defects of the heating system in A's house discovered four months later, and as the furnace was already in use, that F's loss of consciousness may have been caused by inhalation of carbon monoxid to which as the result of her previous exposures and of her recent attack of influenza she naturally would be more susceptible than the other inmates of the house who were in good health. As F was still more or less a stranger in Rochester, it did not seem advisable to allow her to return to her lodgings in a boarding house and she was persuaded to remain at the house of A under medical supervision. During the following weeks F developed a great number of symptoms which completely puzzled her physicians and which have been described elsewhere.65 Periods of comparative well-being alternated in F's case with severe attacks of abdominal pain accompanied by visible spasms of the lumbar and abdominal muscles, attacks of syncope without demonstrable cause, chills and shivering fits without rise of temperature, severe headaches behind the eyes, obstinate constipation and an increasing general weakness with tendency to collapse on slight exertion, accompanied by a slight bronzing over the entire body. There was a total lack of clinical findings, with the exception of an erythrocyte count of 5,000,000, which seemed in absolute disharmony with the condition of the patient. The inexplicable syndrome was put down to "neurasthenia", although this diagnosis failed to explain either the symptoms or their cause. The discovery of the defective furnace in A's house at the end of October, 1919, together with strongly positive tests for carbon monoxid in the blood of A, of the patient and of her nurse finally provided the key to the enigma and proved conclusively that the symptoms of F were connected with chronic carbon monoxid poisoning. At the beginning of 1920 the defective furnace was entirely eliminated and a connection established between the house and the garage by means of which central heating and hot water were furnished in such a way that any further production of carbon monoxid in the house was made impossible.

During 1920 F continued to suffer from severe menstrual disturbances with menorrhagia. Radium treatment was tried, but with unsatisfactory results. At the end of 1920 symptoms suggesting a mild form of peritonitis developed and an exploratory laparotomy was decided on. The consistently high lymphoid defence of F and the satisfactory amounts of split cholesterol in her blood seemed to indicate that her symptoms were caused by an inflammatory process rather than by malignant changes, although the histologic findings after enucleation of the left breast gave cause for apprehension. The operative findings revealed a complete fibrous and cystic degeneration of both ovaries with occlusion of the tubes, uterine myomas and a sigmoid bound down by adhesions. A subtotal hysterectomy was performed. Histologic examination of all the tissues in serial sections failed to show any trace of tuberculosis or of malignant proliferation. Both operative and histologic findings corroborated the indications furnished by the biochemical studies of the blood; they also fully explained the menstrual disturbances, although numerous gynecological examinations by different gynecologists had failed to reveal any definite abnormality; yet every menstruation resembled attempts at walking on a broken leg. It seems warrantable to assume that the changes in the pelvic organs were intimately connected with the presence during twenty years of a chronically inflamed appendix. The marked exacerbation of the menstrual disturbances which followed F's prolonged exposure to carbon monoxid in the house of A may also be connected with the deleterious effect of this gas on several of the glands of internal secretion. The headaches behind the eyes which are characteristic of carbon monoxid poisoning point to the pituitary, since this type of headache is admitted to be associated with disturbances of pituitary function (Halsey, Timme). The transient bronzing, the low blood pressure, low blood sugar values and cardiac irregularities with syncope and progressive asthenia observed in F during her exposure to carbon monoxid recall the manifestations of disturbed adrenal function. According to Evans, "The ovaries appear to maintain definite relations with the pineal, thymus, and adrenal glands, as well as with the thyroid and the hypophysis. . . . Well known is both a castration and pregnancy hypertrophy of the hypophysis while the thyroid is enlarged both at the menses and in gestation".

Evans also mentions that "The cessation of ovarian function is due to a peculiar degeneration of its follicular apparatus - the so-called small cystic degeneration of the ovary"; and he adds: "It is perhaps only fair to say that we are entirely in the dark as to the cause of this abberant behavior of the follicles". It is interesting in this connection that F showed a severe type of menorrhagia for nearly a year although practically complete small cystic degeneration of the right ovary was found at operation and although of the left ovary nothing remained but a single cyst, which was approximately 5 cm., but which could not be measured as it ruptured during the operation; the wall of this cyst was very thin and consisted histologically of an outer layer of fibrous tissue and an inner, single layer of flattened cells.

It may further be of interest to gynecologists that it proved to be possible in the case of F to determine with a fair amount of accuracy the quantity of blood which was lost during the very profuse menses; a determination which presents well-nigh unsurmountable difficulties as a rule. The observation was made that there was no flow except when the patient passed urine and this observation was turned to advantage. A colorimetric scale was obtained by mixing 100 c.c. of water with respectively, 10, 20, 30, 40, 50 and 100 c.c. of blood. The patient's liquid intake and the amounts of urine which she passed were measured very carefully. The amount of blood present in the urine during menstruation (which always lasted eight days at least) was gauged by comparison with the colorimetric standard, allowance being made for the total amount of urine on each occasion, and a daily, very conservative estimate of the total amount of blood was based on these findings. The observations were carried on from January to May and revealed that no less than from 1700 to 2000 c.c. of blood were lost every month. Radium treatment was then given a trial; but although the actual loss of blood diminished by about one-half during the following months, the menses remained very painful and prolonged.

The improvement of the general health of F following hysterectomy was striking and rapid. During the "coal gas period" her weight had dropped to 100 pounds and no amount of care had availed to increase it above 115 pounds, whereas her height according to careful measurement made in various hospitals in London and in Canada was 5 ft. 8½ in; on leaving the hospital in Rochester she weighed 109 pounds, January, 1920 and in August her weight had risen to 130 pounds; she lost

10 pounds during the following months after a tonsillectomy accompanied by pharyngitis; but she regained her weight rapidly; it went up to 140 pounds in the next three months and has remained at that level since. The changes in weight of F following hysterectomy have been discussed in detail because McCrudden (1922) says that, "Surgeons very commonly state that women increase in weight after ovariotomy" and adds, "As a matter of fact examination of carefully carried out studies on several series of cases shows a slight, though possibly insignificant loss of weight". While it is true that many factors coöperated in the case of F to keep her weight far below normal, it is true also that surgical castration is rarely performed on healthy persons. "Glaevecke found a significant increase in body weight in 57.5 per cent of castrated women" (Novak). Far from leading a less active life, F after her operation has been doing a great deal more work as the result of better health.

Another interesting observation made on F should be mentioned. It has already been stated that the records of various hospitals agree in giving her height as 5 ft. 8½ in. During the three years preceding her hysterectomy (December, 1920) it was noticed that her legs, which up till then had been very straight, showed a slight bowing. She also suffered a good deal from pains in her legs, feet and back and her gait was peculiar and unsteady. Several roentgenograms of the spine were taken on the suspicion of an incipient spinal tuberculosis (Quervain); but the findings were always negative. F declared that "troublesome feet" were merely a family failing. Measurements taken by the orthopedic department of the Mayo Clinic (April, 1921) revealed the surprising fact that F had lost a full inch in height and that she was now 5 ft. 7½ in. tall; moreover, the length of her left leg was only 90 cm., while that of the right was 91 cm. It will be recalled that it was also the left ovary of which nothing but a single, thin-walled cyst remained, whereas the right ovary was in a somewhat better state of preservation. The "best portion" of the right ovary according to the surgeon was used for implantation under the rectus muscle at operation, the remainder showed microscopically an extensive fibrous-cystic degeneration. Whatever the correct interpretation of these findings may be, the findings themselves are noteworthy. Dieffenbach, the radiologist of the Community Hospital in New York, in his paper "Osteomalacia, is it a rare or rather common disease?" (1920), calls attention to the characteristic gait in osteomalacia, "the short, unsteady step, with back bent and head forward"; a definition which accurately describes F's way of walking. Dieffenbach also brings out evidence for his belief that "many lesions of osteomalacia (the milder forms) escape unnoticed until they become chronic and are then relegated to chronic invalidism". McCrudden shows that whereas the evidence "is strongly against the hypothesis that osteomalacia is a disease of the ovaries", numerous reliable data are available to prove that "in osteomalacia we are dealing with extreme grades of a normal process", namely the anabolisms and catabolism of bone formation, which goes on throughout life and which is controlled by calcium metabolism. McCrudden says in this connection: "How widely different the nature of the factors responsible for abnormal bone metabolism may be, may be judged from the fact that apparently reliable evidence involves not only pregnancy, but bacterial infection, glands of internal secretion, arteriosclerosis, certain food stuffs, absence of vitamines and starvation or undernutrition", and further, "The evidence connecting osteomalacia with the parathyroid glands is the result of studies carried out in Professor Weichselbaum's laboratory in Vienna, and is stronger than that connecting the disease with any other gland".

The history of F furnishes an interesting example of the coöperation of most of the factors referred to by McCrudden: it contains ample evidence of chronic infection and of factors leading to undernutrition, including severe menstrual loss of blood and the deleterious effect on the organism of prolonged exposure to small amounts of carbon monoxid; while loss of height amount to one inch in an adult can hardly be interpreted otherwise than as a manifestation of abnormal bone metabolism. Circumstances, unfortunately, made it impossible to study the calcium metabolism of F, but the administration of calcium lactate* proved strikingly beneficial in reducing the severity of the tremor, the muscle spasms and the uncontrollable attacks of shivering which developed in both A and F during the "coal gas period"; calcium was used on purely empirical grounds, because the tremor and the muscle spasms recalled the manifestations of parathyroid insufficiency in postoperative tetany (in which calcium is known to be beneficial) and in Parkinson's disease (Barker, 1922 and McCallum). Barker says "Very recently (1920) evidence has been brought by Collip and Backus of Canada and by Grant and Goldman of St. Louis that tetany can be produced experimentally in human beings by forced respiration and that this tetany is associated with a definite alkalosis"; the extensive studies of Henderson and his collaborators, which are summarized in a paper by Henderson and Haggard (1922) on the treatment of carbon monoxid asphyxia by means of oxygen plus carbon dioxid, prove conclusively that there is "an initial overbreathing" during exposure to carbon monoxid, caused by oxygen deficiency, and resulting in "a condition of extreme acapnia", which was "for a time erroneously regarded as an acidosis, whereas it is rather an alkalosis and involves corresponding disturbances in the equilibrium of blood and tissues". The interrelation of the independently gathered data seems worth considering.

It is further of interest that F has had much less trouble with her feet since her hysterectomy, although she is "on them" a great deal more; her gait has become much more steady and she walks more erect. Many factors are likely to have contributed to this improvement, but very recent measurements by our orthopedic department (September, 1922) show that the apparent straightening of the left leg is not wholly imaginary, for both legs are not of equal length, namely 91 cm.; the total height of F, however, has remained 5 ft. $7\frac{1}{2}$ in. Several considerations suggest themselves in connection with these findings, and may help to explain them.

* The classical experiments of Erdheim, showing that removal of the parathyroids in young rats led to disturbances of bone formation resembling those in rickets and in osteomalacia, will be recalled in this connection.

According to McCrudden's conception of bone metabolism both constructive and destructive processes go on side by side throughout life. This conception is supported by Dibbelt's observation that "when recovery from osteomalacia, experimentally* produced in pregnant dogs, takes place, the decalcified bone substance present in the active stage does not later become calcified; it is absorbed and replaced by <u>new</u> calcified bone" (McCrudden). The observation was also made during prolonged studies on a patient with osteomalacia (McCrudden's Table 23) "that after removal of the ovaries, and at the time when the patient showed marked clinical improvement, union of an ununited bone, the result of an osteotomy, took place" (McCrudden). Both of these observations suggest that F's loss in height may be caused chiefly by a mild, slow form of decalcification in the bones of spine and pelvis, affecting the bones of the left leg in a minor degree only; so that after the elimination of the various factors promoting the mismanagement of calcium metabolism, the process of reconstruction soon became visible in the leg, but was less noticeable in spine and pelvis which represent a much wider area. It is also conceivable, on the other hand, that the bowing and shortening of F's left leg was referable rather to weakness of the ligaments than an actual softening of the bones; in this case the straightening and lengthening of the leg might simply be the result of a healthier condition of the ligaments caused by her general improvement, but the persistent loss of height is against this interpretation.

McCrudden points out that it is "only after a long continued and severe drain on the bones of a poorly nourished patient that the body fails to respond to the demands on it, and even then recovery follows if the severe demands are not continued". He shows that it is for this reason that the osteomalacia of pregnancy may be completely cured by castration, which prevents further pregnancies, whereas in spontaneous osteomalacia "castration is not always followed by cure", recurrence being the rule rather than the exception. It would seem that for F the drain on the body during each menstruation represented the "severe demands" to which

* By a diet so low in calcium as to produce osteomalacia in the mother, although the puppies developed normally in utero.

McCrudden refers, on account of the severe damage to the pelvic organs which was only discovered at operation. The improvement of F after hysterectomy is thus fully accounted for. Her case is an example of the unsuspected minor forms of osteomalacia, which, as Dieffenbach says, may "escape unnoticed" until they are relegated to chronic invalidism.

F has not shown any symptoms of premature menopause during the two years which have elapsed since her hysterectomy. It is, of course, impossible to determine whether this is the result of the persistence of the small ovarian graft implanted under the rectus muscle; to the careful administration of organotherapy according to the needs of the patient, in so far as these could be gauged by daily observation; or to other unknown factors. At operation the surgeon selected "the best portion" (macroscopically) of the right ovary for implantation, but the remainder of the gland showed microscopically complete fibrous-cystic degeneration. Marshall and Jolly found a transplanted ovary normal after fourteen months in their studies on rats (Vincent); but no observations seem to be on record for human beings. Graves (1917) believes that the retention of ovarian tissue after hysterectomy is of little physiologic value and may be productive of serious harm; an opinion shared by few observers. Novak (1922) in speaking of the natural menopause, says "In other cases, again, the endocrine apparatus adjusts itself smoothly and rapidly to the withdrawal of one of its cogs, so that there may be scarcely a symptom produced". He also says: "I have myself been impressed with the slight degree of disturbance often following castration when this is made necessary in very young women. The personal equation appears to be a primary factor in regulating the severity of the symptoms, just as in the case of the normal menopause". That the removal of severely battered cogs in the case of F was likely to prove beneficial is obvious; broken, but revolving, cogwheels usually create havoc in any kind of machinery.

A detailed account of the organotherapy used for F cannot be attempted, because all the "little" observations of which a daily record was kept for three years would have to be discussed in connection with the choice of medication. It may be sufficient to state that dessicated gland preparations were given by mouth only and that parathyroid combined with calcium, total suprarenal, corpus luteum and total ovary, thyroxin and total pituitary were used either combined or singly, as seemed indicated. The dosage was very much smaller than is usually considered necessary, because as I have pointed out the body appears to work with incredibly small quantities of its important chemical constituents, and F responds to very small amounts of any kind of medicine. It seemed advisable, therefore to err on the side of safety. In the main pluriglandular therapy was employed, because pressure on a single cogwheel seems likely to put a strain on the rest of the machinery. It is but too true that we are still woefully in the dark concerning innumerable features of organotherapy and that the interrelation and interactions of the glands of internal secretion are but partially known. It is probable also that the endocrine system of different persons, or of the same person at different times, presents "different constellations" to the physician, much as the starry heavens do to the astronomer when one or another of the planets is in the ascendency. All of these considerations make it imperative to use organotherapy with the utmost caution; and few physicians have the unusual opportunity of studying a patient daily, without interruption for three years. Friedrich von Müller to whom Garrison refers as "perhaps the most scientific teacher of internal medicine today" never tired of reminding his pupils that "to do no harm" is the foremost duty of the physician; his "nil nocere" has guided me in the administration of organotherapy to F. Whatever the correct interpretation of the results, an interpretation which in view of the many factors involved would seem unattainable, the fact remains that those who knew F before she came to Rochester, all agree that her health shows a striking improvement; this suggests at least that the methods employed have not been detrimental.

The family history of F furnishes interesting and unusually complete data as regards longevity and the factor of heredity in neoplasia. Her paternal grandfather died at the age of eighty-three from "kidney trouble", and her paternal grandmother at eighty-five from old age and pneumonia. One of her paternal aunts, who lives in Europe, is reported to have had a severe operation for carcinoma. Her father contracted phthisis during the South African Campaign (1892); he developed severe mental disturbances shortly after, but lived for twenty years, and died according to necropsy findings of tuberculous peritonitis at the age of fifty-eight; it seems probable that his mental condition was the result of the tuberculous infection. F never came into contact with her father after he developed tuberculosis. Her only brother died in infancy from some acute form of meningitis.

The maternal great grandmother died of old age at eighty-six years of age; her maternal grandfather was found dead in bed at about thirty years of age, the cause of death is unknown; a sister of this grandfather died of apoplexy and one of his brothers was completely crippled by arthritis deformans at an early age, though he lived to be an old man. These facts recall the relation of arteriosclerosis, arthritis and osteomalacia mentioned by McCrudden. A maternal great, great aunt died of cancer of the breast at the age of sixty; a maternal great aunt of cancer of the breast at the age of fifty-five; F's maternal grandmother died at eighty-four years of age from acute bronchitis; her mother had an operation for a benign tumor of the breast at the age of forty-seven, but is alive and well, although she has to be careful in her diet on account of a tendency to gout; F had an enucleation of the breast for fibro-adenoma at the age of thirty-one.

The occurrence of neoplasia in the same organ during four generations (great, great aunt, great aunt, mother and daughter) and the fact that malignancy became manifest at an earlier age and with decreasing malignancy in each succeeding generation supports the observations of Slye (pages 130-133, Part I) and her conclusion that malignant growth behaves like a recessive according to the Mendelian laws.

Evidence that the Mendelian laws apply to human beings as well as to mice is by no means lacking. The detailed geneologic trees of "cancer families" presented by Brocca, Warren, Saalfield, Pel of Amsterdam and of Warthin are given here because visible data are more easily remembered than mere words and because definite positive findings are more conclusive than apparently negative ones (Tables 15 to 25). It is always difficult to obtain reliable information concerning the heredity factor in human beings, negative findings, therefore, are usually either the result of incomplete data or they may be an illustration of the fact that accidental conditions which only affected a given person were responsible for the development of malignancy. It has been shown throughout this work that the biochemical conception of malignancy offers a logical explanation of both hereditary and accidental manifestations of malignant growth.

Warthin (1914) says in his paper on "Family susceptibility to cancer"; "It is in these detailed family histories that the evidence of a family tendency to cancer stands out". His observations are based on 1600 cases of carcinoma examined at the pathologic laboratory of the University of Michigan between 1895 and 1913. He also says in a previous paper (1913) in which the geneologic trees are given: "Levin considers resistance to cancer a dominant character, whose absence creates susceptibility to cancer. . . . An increased susceptibility therefore becomes the abnormal character of importance and our investigations should be carried along the line of attempting to determine just what lies back of this susceptibility"; biochemical investigation alone would seem able to throw light on the factors which determine this susceptibility. The findings of Warthin are in perfect accordance with the later experimental observations of Slye, and it is well, in this connection, to recall the words of Slye (1920): "If scientists . . . . would concentrate their attention on the following facts in heredity, they would find encouragement not hopelessness in the unquestionable fact of heredity in cancer: (1) in hybrid crosses cancer and noncancer tendencies <u>segregate out</u>, and are transmitted as such, (2) all human matings are hybridizations, and (3) cancer behaves as a recessive".

The family history of F is a striking illustration of the foregoing statements. The personal history of F, with its many complicating factors,

Table 15.
CANCER FAMILY OF MADAME Z

I. Generation. Madame Z died 1788 of cancer of the breast, sixty years of age

Four daughters (A, B, C, D)

II. Generation.	A died of cancer of the liver, 1820, sixty-two years of age	B died of cancer of the liver, 1805, forty-three years of age	C died of cancer of the breast, 1814, fifty-one years of age	D died of cancer of the breast, 1827, fifty-four years of age
III. Generation.	Three daughters alive at Brocca's time, aged sixty-eight, seventy-two, and seventy-eight respectively	Five daughters and two sons One son died of cancer of stomach, aged sixty-four Four daughters died of cancer of breast One daughter had no cancer, died at the age of sixty-eight. One son had no cancer, died at the age of twenty-eight (None had children)	Five daughters and two sons. One son died in battle, no children One son well, aged seventy-two, two children: One son died of stroke One daughter well, twenty-four years of age One daughter died of cancer of breast, thirty-four years of age, two sons and three daughters: One son died in battle One son well, aged fifty-eight years, three healthy sons. One daughter died in childbirth One daughter died of cancer of breast, aged forty-nine years, two healthy daughters. One daughter died phthisis, aged forty-one years One daughter died of cancer of breast, aged forty years (1822) One daughter died of cancer of uterus, aged forty-seven (1837) unmarried One daughter died of cancer of breast aged fifty-five(1848)two healthy sons One daughter died of cancer of liver, aged sixty-six (1856) unmarried	One son alive and well in Brocca's time

(Brocca, Wolff I, 363).

Table 16.

SAALFELD'S "CANCER-DIABETES FAMILY-TREE

Husband, died of diabetes --- Wife, cause of death unknown

Daughter - husband, diabetes

Daughter, diabetes and phthisis — Daughter, diabetes and GASTRIC CANCER — Son, diabetes and LIVER CANCER — Son, diabetes and GASTRIC CANCER

1 son and 2 daughters (all diabetes)

(Wolff: Deutsch. med.Wchnschr.

Table 17

CANCER FAMILY I

Parents, cause of death ?

Son CANCER OF NOSE — Son CANCER Visceral? — Son CANCER Visceral? — Son - 40 CANCER OF STOMACH

Husband +90, Wife, cause of death ?

Daughter +86 WELL — Son +70 CANCER OF FACE — Son +60 CANCER OF FACE and tongue

Daughter WELL — Daughter WELL — Daughter WELL — Daughter WELL — Son CANCER OF ESOPHAGUS — Daughter WELL — Daughter CANCER OF STOMACH — Daughter WELL

Daughter WELL — Daughter CANCER OF STOMACH

(Pell, P.K.: Berl. klin. Wchnschr., 1915, lii, 288-289).

Table 18

CANCER FAMILY II

Husband + 36 pleurisy — Wife + 85 old age

Son + 64 GASTRIC CANCER — Son + 60 GASTRIC CANCER — D + 43 GASTRIC CANCER — D + 56 GASTRIC CANCER — Son + 56 GASTRIC CANCER — Son 60 WELL — D 68 WELL

"Stomach trouble"

(Pell, P. K.: Berl.klin.Wchnschr., 1915, lii, 288).

Table 19.

CANCER FAMILY III

Grandmother: CANCER OF BREAST

Daughter: CANCER OF BREAST

Daughter
CANCER OF BREAST

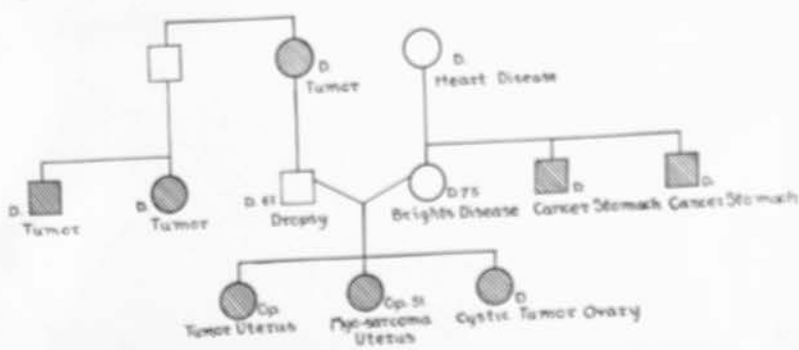
Daughter
CANCER OF BREAST

Daughter
CANCER OF BREAST

(Pell, P.K.: Berl. klin. Wohnschr., 1915, lii, 288).

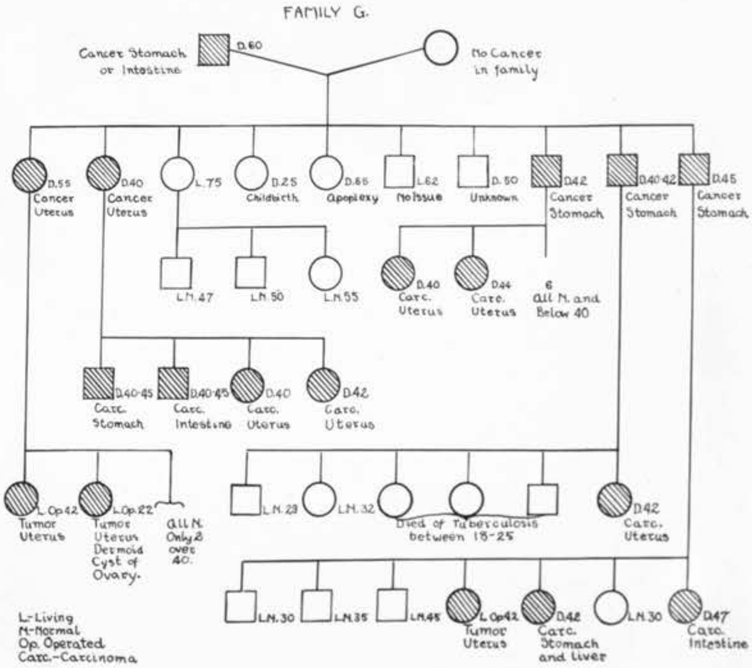
Table 20.

FAMILY F.



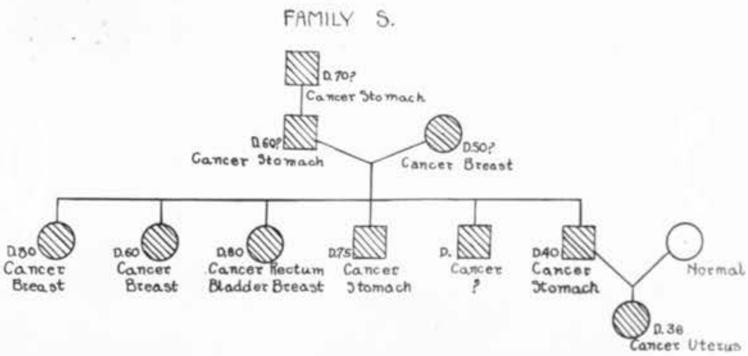
Warthin A.S. Arch. Int. Med. 1913 XII 546-555

Table 21.



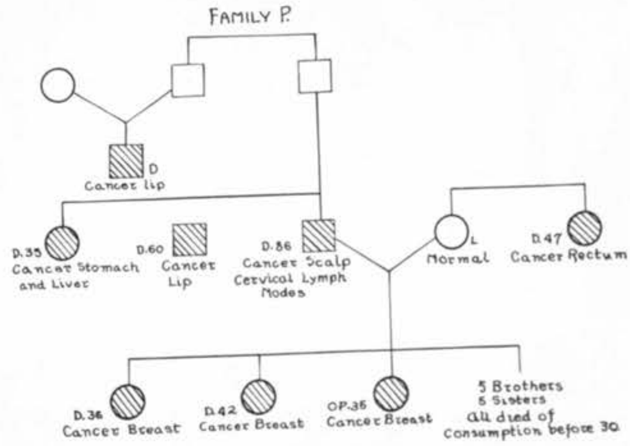
Warthin A.S. Arch. Int. Med 1913 XII 546-555

Table 22.



Warthin A.S. Arch. Int. Med. 1913 XII, 546-555

Table 23



Warthin A.S. Arch. Int Med 1913 XII, 546–555

Table 24

Table 24

CANCER FAMILIES

Bonaparte Family

Mother, CANCER OF BREAST Father, CANCER OF STOMACH, Sister, CANCER OF STOMACH

Twin Twin (died childless) Napoleon I, CANCER OF STOMACH Daughter, phthisis

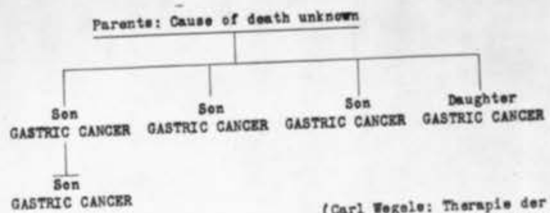
Daughter, CANCER OF BREAST

Child, CANCER OF STOMACH

Twin Twin Daughter, CANCER OF STOMACH

Table 25

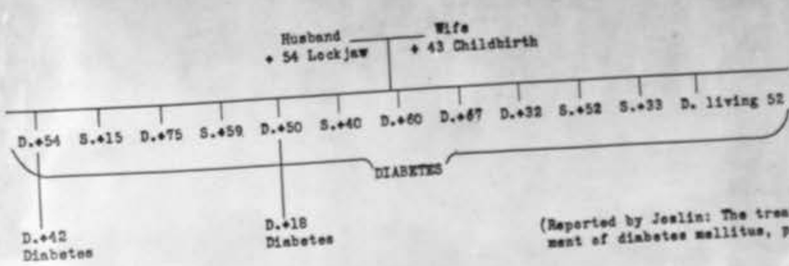
CANCER FAMILY



(Carl Wegele: Therapie der Magen- und Darmerkrankungen. Jena, Fischer, 1905).

Table 26

DIABETIC FAMILY



(Reported by Joslin: The treatment of diabetes mellitus, p.46).

has been analysed in detail in the hope that it may furnish some clues in the case of other patients whose symptoms also present "medical conundrums" to their physicians.

The relation of the total leukocyte counts to the blood cholesterol values

When two curves, representing two blood constituents, consistently show the same type of variation for a period of seven years in tests made on the blood of one person, and when the behavior of the curves is identical for long periods in determinations on the blood of many other persons, it seems reasonable to conclude that a certain relation exists between the blood constituents in question.

A comparative survey of the charts (Figs. 23 to 44) shows a practically constant, <u>inverse</u> relation between the unsaponified, Bloor I cholesterol (heavy solid line Bloor I) and the total leukocyte counts (thin solid line W.C.). How is this inverse relation to be accounted for? The blood samples for counts and chemical analysis were always taken well-nigh simultaneously, before breakfast, the blood for analysis being taken from the cubital vein, that for the blood counts from the ear in every instance.

At first sight the explanation of the inverse behavior of the leukocytes and the blood cholesterol seems simple enough. Cell destruction, the disintegration of the leukocytes in the blood stream or elsewhere appears to account for the phenomenon that high leukocyte counts accompany low Bloor I values and that a decrease in the number of leukocytes goes hand in hand with higher cholesterol values. On second consideration, however, unsuspected problems present themselves for the following reasons:

1. I have pointed out that radium treatment, which admittedly produces an intensive cell destruction, is not accompanied by a rise but a drop of the Bloor I cholesterol, when the patient responds to the treatment.

2. A very considerable drop of the leukocytes during an interval

of a few days or a week at the most, is followed only by an insignificant rise of the blood cholesterol. Thus, for example in Figure 24 (1917, October 16 to 31) the leukocytes drop from 19,000 to 6,400, yet the cholesterol only increases from 95 to 110 mg., an increase which is far smaller than that which occurs during the digestion of a hearty meal; in Figure 26 (1918, July 23 to 31) the total leukocytes decrease from 20,000 to 12,000, but the increase of the cholesterol is merely from 94 to 111 mg.; while in Figure 27 (1919, July 24 to 26) the leukocytes drop only from 21,200 to 16,000, whereas the cholesterol jumps from 105 to 165 mg., that is from normal to a decidedly high cholesterol value, although the process of digestion is entirely excluded in these determinations. Similar findings occur in the other charts; it would take too long to refer to each individually.

3. Nevertheless, in all of the charts, a high peak of the thin leukocyte line will be found, almost invariably, opposite a low dip in the heavy cholesterol line. These facts suggest that mere cell destruction fails to account for the inverse relation of the leukocytes and the cholesterol values. It seems possible that other factors which influence both cholesterol metabolism and leukocytosis might help to explain these findings; the correlation of such factors is the object of this paragraph.

Although our present knowledge of suprarenal activities is far from complete many independent observations furnish evidence that both the blood leukocytes and the blood cholesterol are influenced by a common factor; the suprarenal gland as a whole. But the suprarenal is a duplex gland, composed of medulla and cortex; the component parts, although inextricably joined in man, attend to different functions. The medulla appears to be chiefly concerned in the production of epinephrin; the cortex is intimately connected with lipoid metabolism.

No attempt has been made so far as I know, to study the interaction of medulla and cortex; the result, for example, of increase cortical activity on the production of epinephrin. In man such investigations would doubtless be associated with unsurmountable difficulties; in certain lower animals such as fishes (Cowdrey) in which cortex and medulla have not amalgamated the attempt might not be doomed to failure.

It has been suggested that substances elaborated in the cortex are passed on to the medulla, there to be converted into epinephrin, or, "that epinephrin might be derived from decomposition products of the cortex (Burrutan, Crawford). The work of Stewart and Rogoff indicates that the epinephrin furnished by the suprarenal medulla is not essential to life; animals in which one suprarenal had been extirpated and the other denervated and whose blood but 1:75,000,000 epinephrin was demonstrable (the test used by Stewart and Rogoff reveals the presence of epinephrin in a dilution of 1:330,000,000) lived and appeared to be in perfect health until killed at the end of nine and one-half months. As a rule, in higher animals extirpation of both suprarenals is followed by death in a few days, although "more than 20 per cent of rabbits and 50 per cent of rats survive" (Stewart). The explanation of this phenomenon is a matter of dispute. Sajous emphasizes the occurrence of "abberant or accessory adrenal tissues" and of " a large systemic supply or a reserve of adrenalin". According to Schmorl accessory suprarenals are found in about 92 per cent of human cadavers (Cohoe). Whatever may prove to be the correct interpretation of the persistence of life in spite of a demonstrable reduction of epinephrin, the following findings show that epinephrin influences, activates and mobilizes the blood leukocytes and that the adrenal cortex plays a prominent part in the management of the blood cholesterol.

<u>Epinephrin and the blood leukocytes.</u> According to Hoskins (1922): "The available evidence as a whole indicates that epinephrin produces as its only significant effect a concentration of the spleen, which plays some part in the general shift of the blood from the splanchnic area to the outlying circulation. . . . . Epinephrin is also said to be useful in driving blood infested with malarial parasites from the spleen into the general circulation, thus facilitating their detection". Hoskins and Gunning (1917) kept the spleen in a state of uniform contraction by infusion of adrenalin (0.5 c.c. of a 1:2,000,000 dilution); they

came to the conclusion that "the spleen is one of the most sensitive organs in the body". Frey and Hagemann (1921) obtained a marked lymphocytosis twenty minutes after injection of 1 mg. of adrenalin; they look on the lymphocytic reaction as positive when the number of lymphocytes increases by at least 2,500 cells and as negative when the increase is less than 1,500 cells; they found pathologic changes in the spleen in all cases in which the reaction was negative; after removal of the spleen the injection of adrenalin failed to produce any lymphocytic reaction.

The factors which control the output of epinephrin and its concentration in the blood are still a matter of much controversy. According to Cannon (1922) the discharge of epinephrin is an emergency function; he says: "Thus far no reliable evidence has been brought out by any investigator that there is any secretion of the suprarenal glands under quiet, peaceful conditions". According to Stewart (1922), "a demonstrable amount of epinephrin is invariably present in the blood of the suprarenal veins. . . . while the output (of epinephrin) remains constant, the concentration of epinephrin in the suprarenal vein blood may undergo great variations". It is admitted that the adrenal vein blood is poured into the general circulation; changes in the concentration of epinephrin in the suprarenal vein, no matter what causes them, would seem bound to produce similar, but magnified, changes in the concentration of epinephrin in the general circulation. If, for example, the concentration of epinephrin in the suprarenal vein increased merely from 1:800,000 to 1:500,000 (and far greater variations were observed in Stewart's experiments) even a hypothetical tenfold dilution by the total blood volume would magnify the variation tenfold, causing the concentration of epinephrin in the circulating blood to change from 1:8,000,000 to 1:5,000,000.

Stewart says very definitely that: "Small as the concentration of epinephrin may be in the arterial blood, there is evidence that it may exert a certain action". The experiments of Stewart and Rogoff prove that the minute, spontaneously liberated amounts of epinephrin which enter the circulation at the normal rate of output (when the upper clamp of the vena cava is released) are capable of producing a demonstrable effect on the heart; the work of Hoskins and Gunning shows the great sensitiveness of the spleen to adrenalin; Frey and Hagemann found that splenectomy abolishes the mobilisation of lymphocytes by adrenalin injections. The corroborative evidence contained in the foregoing independent observations supports the deduction that any factor tending to produce variations in the concentration of epinephrin in the suprarenal vein, will also affect the concentration of epinephrin in the circulating blood, find an echo in the spleen, and help to produce fluctuations in the number of circulating leukocytes, such as have been reported by Mauriac and Cabanat.

A discussion of the many factors which might bring about the "great" variations in the concentration of epinephrin in the suprarenal vein, mentioned by Stewart, would be out of place in this work, but an observation made on myself may be of interest as it corroborates the findings of Mauriac and Cabanat; and because it is supported by the observations of Grawitz, Wagner and Rosenthal on the so-called "myogenic leukocytosis", the leukocytosis resulting from muscular activity, while it might be accounted for by the variations of epinephrin concentration in the circulating blood.

As a preliminary study for investigation of the effect of thyroxin on the total leukocyte counts, I decided to make daily counts on myself for a week, the samples being taken in bed on waking, then after dressing and finally on arrival in my laboratory; all of the samples were taken from the ear and "on an empty stomach". The information thus obtained proved to be somewhat disconcerting and caused investigation of the effect of thyroxin on leukocyte counts to be abandoned. Technical errors had been successfully excluded by using the same pipettes, by taking several samples and by using the average of several counts in every instance, although the figures in the same group of samples did not vary by more than 200 cells at the most. The total counts* obtained from samples taken in bed and after dressing did not show any marked variation, but those obtained on

* No attempt was made in these counts, unfortunately, to determine the relation of the lymphocytes to the polymorphonuclear leukocytes; but Grawitz mentions the predominance of a lymphocytosis.

arrival in the laboratory, after driving a car through the chilly morning air (the experiment was done in autumn) for a distance of barely half a mile, showed a two or threefold increase of the leukocytes. The mere fact of driving through the morning air and the negligible amount of muscular effort required to steer an automobile for a short distance on paved roads, therefore apparently caused a mobilisation of blood leukocytes into the peripheral circulation. Grawitz mentions that in Dr. Wagner, whom he describes as "exceptionally healthy and remarkably strong muscularly" the leukocyte counts changed from 7,500 to 11,200 after rowing exercises had been done for a brief period; in somewhat debilitated patients the counts rose from 4,400 to 11,700 under the same experimental conditions. In my experiment the variations were found to range from 6,500 to 14,000 and 18,000, although it would seem that "debility" might be excluded as the cause of the phenomenon; for, as has been stated (see clinical history of A) I appear to possess a rather unusual degree of resistance and immunity to bacterial infection and my muscular strength "graphic", according to experimental tests made with the Universal Dynamometer at the Battle Creek Sanitorium, shows an excess of 36 per cent above the average for my height, weight and age; it might be of interest to mention also that, being a European, I have smoked many cigarettes daily for the last thirty years, but that none were smoked till after the counts in the laboratory had been taken.

It is admitted that there is "a close relationship between the suprarenals and muscular activity . . . . there is evidence that epinephrin may be of importance in muscular fatigue" (Hartman). Injections of adrenalin have been found to delay fatigue of the skeletal muscles; the quantity of epinephrin in the suprarenals has been observed to be greatly diminished and the cortex vacuolised through the disappearance of "the lipoid-cholesterol bodies after intense prolonged muscular activity" (Hartman). This evidence, taken in conjunction with the findings concerning mobilisation of the leukocytes by both adrenalin and muscular activity, seems to establish a link between the constant fluctuations of the circulating leukocytes even in healthy persons, reported by Mauriac and Cabonat and shown by my experiment, and the variations of the epinephrin concentration in the suprarenal veins, emphasised by Stewart. This is a matter of more than theoretic importance. If there is a tendency to a "personal leukocytic level" in different persons, and the charts of B (Figs. 33 to 36) and of D (Figs. 40 to 41) show a persistently low level during several years, while those of A (Figs. 23 to 32) reveal a tendency to high leukocyte counts, and if slight muscular exertion is capable of causing a marked leukocytosis in healthy persons, then the diagnostic value of leukocyte counts, taken according to the usual routine procedures of clinical investigation, would seem rather questionable when ambulant patients are concerned. It is obvious that in persons with a habitually low leukocytic level of 3,000 to 4,000, a count of 10,000 might represent a pathologic leukocytosis. On the other hand the finding of 16,000 leukocytes, when intercurrent factors such as the effect of muscular activity, exposure to carbon monoxid or even the tardy influence of digestion are not considered, would be well calculated to throw suspicion on a wholly innocent appendix, unless the "council for the defence" of said appendix was able to submit evidence of "normal" counts in the absence of muscular activity and of any effect of the digestive process. The hourly fluctuations of the leukocyte counts found by Mauriac and Cabonat in their careful studies on themselves recall the fluctuations of the basal metabolic rate, and determinations of basal metabolism are never made without the necessary precautions for the elimination of intercurrent factors.

<u>The suprarenal cortex and the blood cholesterol.</u> The substances of which the suprarenal cortex is chiefly composed have been grouped together under the name lipoids. Many of these substances differ from the true fats in their histologic staining reactions; they fail to take the usual fat stains; they readily dissolve in chloroform and they are double refractile under the microscope. Crawford (1922) points out that "the term 'lipoid' must necessarily be rather indefinite and embrace a number of ill-defined substances".

Iscovesco (1922) whose extensive studies on the lipoids began in 1908, has recently summarized our knowledge of these bodies. He suggests that the term lipoid is incompatible with the progress of modern chemistry; since we no longer speak of "albuminoids" but of proteins, we should use the term "adepoids" to designate the whole group and retain the word lipoid only for such of its derivatives as have been isolated in pure form. The adepoids, although fat-like in appearance, are no more "fats" in a chemical sense than vaselin for example. The true fats contain but three elements (carbon, hydrogen, oxygen); but the molecules of the adepoids are much larger than those of the true fats and contain at least four elements (carbon, hydrogen, oxygen, nitrogen), and generally five (carbon, hydrogen, oxygen, nitrogen, phosphorus). The adepoids are composed of one or more fatty acid radicals and of one or several nitrogenous bases; they may contain phosphorus or sulfur or both. It would seem that the different nitrogenous bases which are attached to different lipoids determine their individual, characteristic properties. Lipoids isolated in pure form were used in all of Iscovesco's experiments; and the latter proved that lipoids isolated from specific tissues (heart, ovary, brain, placenta, corpus luteum, erythrocytes, thyroid and suprarenal cortex or medulla) have a specific affinity for the organs from which they are derived. Iscovesco showed, for example, that the administration to animals of lipoids extracted from the adrenal medulla produced an increase in size of the suprarenal glands and of the heart as well as a very slight increase in the size of the kidneys; whereas administration of lipoids derived from the cortex failed to affect the heart and the kidneys, but caused some hypertrophy of the suprarenals together with disturbances of growth of hair and skin pigmentation. Similar results were obtained by feeding five different preparations of cortical extracts to 118 animals by Hewer (1922) at the London Royal Free Hospital; the detailed account of the histologic changes in numerous organs should be read in the original, as an abstract would fail to do justice to Hewer's work.

Cholesterol, according to Iscovesco's findings, always accompanies the lipoids and appears to have a neutralizing, or stabilizing, a restricting or intensifying influence on their activities; its effect depends on the individual characteristics of the lipoids which are involved in a given reaction; but cholesterol is not a lipoid, it is an adepoid with the chemical behavior of an alcohol. Many organs, the liver, the thyroid, the pancreas, the gonads and possibly others, influence the blood cholesterol. All available evidence, however, points to the suprarenal cortex as the chief regulator of cholesterol metabolism.

"In dry human suprarenal Wells found 36.3 per cent of material soluble in ether, of which 22.06 per cent was cholesterol" (Crawford, 1922). The experiments of Sternberg (1915) prove that cholesterol administered by mouth is stored in the suprarenals; Sternberg produced by cholesterol feeding to male rabbits a cortical hypertrophy entirely similar to that found in female rabbits without cholesterol feeding during pregnancy; his findings support the contention of Cramer (1920) that "the lipoids do not represent the internal secretion of the cortex as they are not formed in the cortex, but taken up by it from the outside . . . . the cortex is the channel by which they pass to their destination" (Crawford). In my experiments on goats a very marked rise of the blood cholesterol was obtained in two males by cholesterol feeding alone and the controls did not show this increase. No attempt was made to determine the cholesterol content of the suprarenals in these animals, because both biochemical and histologic data on goats are lacking to the extent of rendering comparison impossible. The blood cholesterol determinations, on the other hand, which were done weekly on nine goats for several years seemed to offer reliable and comparable findings; but total leukocyte counts on goats give very unsatisfactory results, because it is practically impossible to exclude the influence of digestion in ruminating animals and the withholding of food for a sufficiently long period would complicate the interpretation of the findings by introducing symptoms of starvation, which alters the cholesterol values.

A brief summary of the evidence presented brings out the following facts: (1) the amount of epinephrin in the circulating blood is incredibly small, yet it is capable of exerting demonstrable effects and the spleen is particularly sensitive to epinephrin, (2) the effect of epinephrin on the spleen is accompanied by a mobilisation of leukocytes into the blood stream, which is abolished by splenectomy; (3) muscular activity causes fluctuations in the number of circulating leukocytes, which appear to be connected with fluctuations in the epinephrin concentration of the blood, since excessive and sustained muscular exertion leads to a demonstrable depletion of the suprarenal medulla as well as of the cortex, whereas muscular fatigue may be delayed or abolished by injections of adrenalin, and (4) the suprarenal cortex contains a considerable amount of cholesterol; it is capable of storing cholesterol and it appears to be either the chief regulator, or at least one of the most important organs of cholesterol metabolism, a deduction which is further supported by the observations made on the blood of double adrenalectomized dogs (Chapter XI). (5) Mann (1922) refers to the spleen as "the largest reservoir of lymphocytes in the body", and it is noteworthy that the leukocytic reactions caused by epinephrin injections and abolished by splenectomy as well as the leukocytosis produced by muscular exertion (Grawitz) were predominantly lymphocytic in character. It should be borne in mind also that my diagrams refer to total leukocyte counts, in which unfortunately no attempt was made to establish the relation of the lymphocytes to the polymorphonuclears, because my studies on the interrelation of blood constituents were not undertaken with the object of proving or disproving anything, but merely for the purpose of making observations; however, the "lymphoid defence" will be found relatively high in nearly all the diagrams in question. Mann states further that "The results from the effect of splenectomy on the leukocytes are not in accord"; and that Johnstone in experimental splenectomy in dogs, "controlling one dog against another . . . . found it impossible to obtain consistent results;" a fact which might be explained by the different degree of reactivity of divers organs in different animals, which, as I have pointed out in previous chapters, is likely to make different individuals comparable to different chemical mixtures. Sivertsen's and Dahlstrom's recent statistics, moreover, suggest the possibility of a relation between lack of muscular activity resulting from the "advent of the age of machinery" and the incidence of carcinoma; in this connection the harmful effects of the combustion products which are associated with most mechanical appliances as well as the lymphocytic reactions and the anomalies of cholesterol metabolism in malignancy may also be worth recalling.

All of the foregoing data suggests that some as yet unexplained interaction between suprarenal medulla and cortex, rather than mere cell destruction, may be responsible for the almost constant occurrence of high leukocyte counts with low cholesterol values (and vice versa) seen in the diagrams. It must be left to future investigations to elucidate the mechanism of the phenomenon, but the structure of the suprarenal gland indicates that interaction between cortex and medulla is to be expected and the diagrams show the persistence of an inverse relation between blood cholesterol values and total leukocyte counts.

The relation of the blood cholesterol to the blood sugar values

The coincidence of high blood cholesterol and high blood sugar values has been observed in divers pathologic conditions: in diabetes, in which "cholesterol constitutes an excellent index of the degree of lipemia" (Myers, 1922); in eclampsia, in which according to Widen the absence of hyperglycemia denotes an unfavorable prognosis, and in which the cholesterol content of the blood shows a considerable increase (Autenrieth and Funk, Slemons, Pisani, Severe, Baily); and in malignancy, according to the observations of Benedict, Myers and Luden.

On the other hand, an increase of the blood cholesterol values may occur in the absence of any disturbance of sugar metabolism, as in arteriosclerosis, nephritis, or cholelithiasis, and in mild forms of diabetes "the blood lipoids (including cholesterol) may be practically normal" (Myers). It has been stated as the result of these findings, that, "Taken as a whole there seems to be no definite relation, as far as can be judged by the analytical data presented, ... between the blood sugar and the cholesterol" (Denis, 1917). This is perfectly true when but a small number of determinations is made on the same person, even though the number of cases studied is large; another factor worth considering is that the findings of Denis are based on the use of the Bloor II (unsaponified) method exclusively; and it has also been pointed out that determinations by the Bloor II method alone tend to furnish conflicting evidence because of the variable amounts of cholesterol split products (pages 149-155, Chapter XII).

Serial observations by Bloor's two methods show, however, that if tests are made for a sufficiently long period of time, even on a relatively small group of persons, a certain relation between the general trend of the blood cholesterol and of the blood sugar curves may be observed. The trend of the curves seems to maintain a definite character in the blood of the same person for a considerable time, in spite of temporary deviations in individual tests; the blood sugar and the cholesterol curves of two different persons may show opposite tendencies, running parallel for the one and inversely for the other; and the curves of a given person may change their general trend and begin to run in opposite directions after having run parallel for several months or vice versa. The behavior of the blood sugar and of the blood cholesterol curves is illustrated by the diagrams of A, B, C, D, and F (Figs. 29 to 44); blood sugar determinations were begun June, 1919; Benedict's new method was used consistently for all the tests.

The sugar and cholesterol curves of A show a tendency to run parallel in Figures 27 to 30, that is from June, 1919 to September, 1920, but they veer to a tendency in opposite directions in Figures 31 to 32, from September, 1920 to June, 1922; those of D and F behave quite differently. The curves of D (Figs. 40 and 41) from July, 1919 to June, 1920 and those of F (Figs. 42 to 44) from August, 1919 to June, 1922 show a general trend to run inversely, while an increasing tendency to parallelism is to be found in the later determinations. It is interesting that in the case of A, according to the notes in the daylog, general fatigue appears to have played a part in changing the tendency of the curves from parallel to inverse; while in D and F the change of the curves towards parallelism was accompanied by a marked improvement in general health. A, after nine week's exposure to the fumes of a defective furnace during the autumn of 1919, experienced during the summer of 1920 the combined effects of extra work and extra worry in connection with a graduate degree and the illness of a friend whom she nursed while preparing for the examination; D and F had both been exposed to the furnace fumes also, they were recovering respectively from several attacks of influenza, and from radium treatment for menorrhagia followed by a hysterectomy when their curves began to change from inverse to parallel.

It cannot be emphasized too strongly that the experimental conditions, under which the tests recorded in the diagrams were obtained, were far from ideal; inasmuch as the enforcement of a uniform diet was out of the question, because the persons on whom the observations were made did not all live under the roof and because they followed different pursuits, apart from being different "personalities" with different "temperaments", resulting presumably from different kinds of chemical combinations; although every effort was made to obtain the blood samples under strictly uniform conditions, and to eliminate all technical errors.

The entertaining, uncomplimentary, and alas, very pertinent criticisms of de Kruif (1922) in "Our medicine men", concerning medical methods of investigation as compared with the exact methods employed by mathematicians and engineers, may be recalled in this connection; but it should be recalled also that the mathematician possesses means of establishing the exact value of the "unknown quantities" in his calculations and that the material analyzed by the chemist does not complicate his problems by being "alive"; whereas observations of the type depicted in the diagrams are handicapped not only by a host of "unknown" factors, but also by the changes which take place in every "living" organism studied for any length of time. Consequently, the questions which present themselves are the following: (1) does the parallel or inverse tendency of the blood sugar and cholesterol curves have any real significance? (2) do the diagrams show any coincident changes in other blood constituents? and (3) is there in other independent observations any evidence suggesting that the behavior of the curves may be indicative of chemical changes within the body, resulting from changes in the activity of certain organs?

The first question will have to be answered last; for the correlation of many findings is needed to explain the behavior of the curves; but it would seem that the questions may be answered in the affirmative on account of corroborative evidence. While such evidence does not constitute conclusive proof, it is usually admitted that an adequate amount of corroborative evidence is sufficient to justify a verdict even in legal matters.

The answer to the second question, concerning changes in other blood constituents coincident with variations in the general trend of the cholesterol and the sugar curves, will be found in Tables 27 and 28.

Table 27.

Diagrams showing tendency to parallel behavior in cholesterol and sugar curves

Diagrams of	Diagrams number	Leukocytes High	Leukocytes Low	Tests, total	Tests with low split cholesterol values Number	Tests with low split cholesterol values Per cent
A:V-VII	3	3	0	56	8	13.2
B:IV	1	0	1	12	0	0
C:II-III	2	2	0	29	4	13.8
F:III	1	0	1	18	2	11.1
Totals	7	5	2	115	16	10.6

Table 28.

Diagrams showing tendency to inverse behavior in cholesterol and sugar curves

Diagrams of	Diagrams number	Leukocytes High	Leukocytes Low	Tests, total	Tests with low split cholesterol values Number	Tests with low split cholesterol values Per cent
A:VIII-IX	2	1	1	29	7	24.1
D:II-III	2	0	2	31	3	9.7
F:I-II	2	0	2	36	4	11.1
Totals	6	1	5	96	14	14.8

The two tables show a slight preponderance (7:6) of the diagrams in which the trend of the cholesterol and sugar curves is parallel and this trend is accompanied by a tendency to a high range of the leukocyte counts (5 high : 2

low). But the most important finding is the increase in the percentage of tests with split cholesterol values, which are below the normal minimum of 17 mg. for each 100 c.c. of whole blood.

It is interesting that although the tables represent only the general trend shown by the cholesterol and sugar curves, regardless of temporary deviations in individual tests, the parallel tendency of the curves should be found accompanied by a distinctly high range of the leukocytes (5 high : 2 low) and but 10.6 per cent of tests with less than the normal minimum of split cholesterol, whereas the tendency of the sugar and cholesterol curves to run in opposite directions is accompanied by a much lower range of the total leukocytes (1 high : 5 low) and by a far greater percentage of tests with subnormal split cholesterol values, namely 14.8 per cent, representing an increase of nearly one-third in the number of tests with split cholesterol values below 17 mg.

The significance of the cholesterol split products in the blood.

If, as has been discussed in previous chapters, the relative amount of split cholesterol in the blood indicates an adequate or inadequate management of cholesterol metabolism, then an increase in the percentage of tests with low split cholesterol values would seem to be an indication that, for some reason, cholesterol metabolism is being handled less efficiently; this is what appears to occur when the cholesterol and the sugar curves tend to run inversely rather than parallel. The question, therefore, deserves to be considered: Is there any evidence to suggest which organ or organs may be suspected of influencing or regulating the amount of cholesterol split products in the blood? The evidence gathered so far is based on four observations of a different character; but this evidence points to the suprarenal glands, as may be seen from the following:

1. In the blood of three dogs (Fig. 45) cholesterol split products were found two weeks after the removal of one suprarenal gland, but the split cholesterol disappeared entirely from the blood, identical values being obtained with Bloor's methods, after the second suprarenal gland had been removed. A very small

amount of split cholesterol reappeared in the blood of the animals when they became moribund; presumably as the result of increased muscular activity or labored breathing during the death struggle, since it is known that exertion of any kind tends to increase the basic metabolic rate and, coincidently, many of the chemical reactions in the body. No lack of split cholesterol, however, occurred in the blood of dogs killed (Fig. 46), even when the condition of the animals was deteriorating rapidly and although the Bloor I (saponified) cholesterol values became very low. The cholesterol and sugar curves of the double adrenalectomized dogs show a tendency to run inversely; those of the liverless dogs a tendency to run parallel.

2. The second observation is connected with changes found in the blood of three patients suffering from Addison's disease, during the administration of adrenalin and total suprarenal gland. The findings are given in Table 29 but they do not represent a clear-cut picture of the behavior of the blood cholesterol in Addisonia, because the patients, with one exception, had been under treatment before the first test was made; certain of the findings are interesting nevertheless.

Table 29.

The blood cholesterol during administration of adrenalin and suprarenal in Addisonia

				Mg. for each 100 c.c. of whole blood				
				Blood cholesterol		Split cholesterol	Sugar	
Case	Name	Test	Date	Bloor I	Bloor II	(Bloor II-I)		Treatment
A386981	P.Y.	I	8/17/22	114	127	13	100	Four months. Adrenalin 8/18/22
		II	8/19/22	125	169	44	95	
A401101	J.L.	I	8/17/22	107	127	20	100	Several days
		II	8/19/22	79	79	0	*	Adrenalin 8/18/22
A400254	I.R.	I	8/17/22	127	148	21	100	No treatment
		II	8/19/22	136	145	9	105	Adrenalin 8/18/22

* Clotting of blood prevented obtaining a sufficient amount; no test was made.

The first two patients were about thirty years old; the last patient was nearly fifty years of age; all of them were given 1 c.c. of adrenalin

(1:1000) hypodermically August 18, 1922 and the blood samples were taken in each instance the day before and after the injection, before breakfast at 8 a.m., whereas the adrenalin was administered during the afternoon of the day intervening between the blood tests. The first patient, however, P.Y., had received treatment for syphilis including arsphenamin injections, potassium iodid and mercury inunctions for three months and total dessicated suprarenal (5 gr. three times a day) by mouth for one month when the first test was made, and his blood still showed total inhibition July 28, 1921. The second patient, J.L., had had adrenalin by rectum and total dessicated gland from August 14 to August 17, 1922 and the tendency to clotting exhibited by his blood, which prevented making a sugar determination, shows that the effect of the adrenalin administered hypodermically some twelve hours before the second blood sample was taken had by no means worn off. The third patient, I.R., had received neither adrenal nor total dessicated gland when the first test was made. Whereas the blood cholesterol split products increased in the second test of P.Y., those in the blood of J.L., which were subnormal dropped to 0 mg., and those in the blood of I.R., the older man, also decreased markedly after the hypodermic injection of adrenalin. These data are not presented in connection with the effect of the treatment, which, carried on for several weeks after the last blood test was made, proved highly beneficial, but they furnish evidence that in two patients, in whose cases the findings are not complicated by prolonged previous therapy, the administration of adrenalin caused a reduction of the split cholesterol, strongly suggesting that the suprarenals play an important part in the regulation of the amount of split cholesterol in the blood. The mechanism of this phenomenon is unexplained; no further observations could be made so far; fatigue on the part of the adrenals following stimulation suggests itself as an explanation. The evidence, however, is meager; it resembles the straw showing the drift of the current; but even straws have proved useful occasionally, as the findings in the blood of the double adrenalectomized dogs seem to indicate.

3. The third observation on the relation of the blood cholesterol to adrenal activity was made during the experimental ingestion of total, dessicated suprarenal gland by A and C between May and August, 1919; that is, about two years before the findings in the blood of double adrenalectomized dogs furnished a more definite clue.

The total amount of dried gland taken by A during three separate experiments was 4,200 mg., while 1,000 mg. was taken by C in one experiment covering five days; Armour's preparation (U.S.P.) was used, which contains according to information courteously supplied by the Armour Company, 0.5 per cent per weight of adrenalin. The correct dose for experimental purposes presented a problem in itself, because both A and C were in excellent health. In cases of Addison's disease Bates obtained a marked general improvement with 15 mg. daily. Sergent has recommended 6 mg. a day only, and Suckling has reported good results from doses as large as 12,000 mg. a day; but Sajous (1919) warned against over-dosage as fatal adrenal hemorrhages have been observed following therapeutic over-driving of the suprarenals. It seemed desirable in an experiment to take enough of the dried gland to produce at least some changes in the blood, yet inadvisable to take too much; for, if it may be said that a dead Indian is always a "good" Indian, a dead experimenter is likely to be useless. In view of these considerations a dosage of 200 mg. daily was decided on and this amount was to be taken for several days, immediately after breakfast, the results being awaited and checked by blood analyses. Details of the experiments are given in Table 30 and the chemical observations made on the blood of A are given in Figures 27, 28 and 29. Figure 28 presents a bird's-eye-view, as it were, of the changes in A's blood during the whole of the year 1919; to make the picture clearer this diagram has been simplified by including only the curves of the blood cholesterol, the total leukocytes, the blood sugar and the coagulation time of the blood; the amount of split cholesterol in the blood is indicated (as in all the diagrams) by broken vertical lines, and subnormal amounts of split cholesterol are designated by a small, heavy horizontal bar above the broken vertical line. Circumstances, unfortunately, prevented chemical analyses of the blood of G.

Table 30.

Experimental ingestion of total dessicated suprarenal substance by A and C, 1919

Date	Dosage mg.	First experiment by A (Daily dose taken 9 a.m.)	Date	Dosage mg.	Experiment by C (Daily dose taken 9 a.m.)
May 27	200	Feels well, exhilarated	May 28	200	Feels well, exhilarated
28	400	Extreme lassitude, 9 p.m.	29	200	No discomfort, energetic
29	200	Feels well, less tired	30	200	Extreme lassitude, 6 p.m.
30	200	"Slept-out" on waking	31	200	Well, far more "slept-out"
31	200	Well, increased energy	June 1	200	on waking, less easily tired
Total	1200		Total	1000	
		Second experiment by A (Daily dose taken 9 a.m.)			Third experiment by A (Daily dose taken 9 a.m.)
June 5	200	During A.M.A.Meeting	July 24	200	Very tired on waking
6	200	Well, no discomfort	25	200	Hands and legs ache, tremble
7	200	Very well, not tired	26	200	Nauseated on waking, tired
8		Pause to watch effect	27	400	Pain around heart, tired
9	200	Very well, busy; no dis-	28	200	Less tired, precordial pain
10	200	comfort whatever	29	200	Better, working long hours
11	200	Taken 10 p.m. (dinner at	30	200	Precordial pain, tired but
		6 p.m.; gastric pain,	31	200	capable of much extra work
		lasting three days	Aug. 1	200	
Total	1200		Total	2000	

Although these experiments were by no means conclusive because the experimenters were handicapped by that "force of circumstances" to which reference has been made at the beginning of the chapter, and because of an intercurrent, at the time unsuspected factor, certain subjective observations and some of the findings in the blood of A (Figs. 27 to 29) are worth mentioning. The intercurrent factor which doubtless vitiated the findings during A's third experiment, to some extent at least, was the defective central heating system in the house of A which remained unsuspected till the end of October. The main furnace was not in use in July, but the small auxillary furnace for the hot water supply burned day and night;

it was heated with coal and found to be the chief source of carbon monoxid production, when the defects of the hot water central heating system were finally discovered. The symptoms of A during the third experiment, namely, lassitude and nausea on waking, precordial pain and pains and trembling in legs and arms (the result of vein spasms as I have explained elsewhere) and general weariness are characteristic symptoms of chronic carbon monoxid poisoning. Transient exposure to automobile exhaust gas still produces these symptoms temporarily in A today (1922), but A can also produce them by taking a sufficient amount of dessicated suprarenal, as has been done several times to check previous findings. These facts make it difficult to decide whether the furnace fumes or the fairly large doses of dried suprarenal were responsible for the subjective discomforts of A during the third experiment. It is noteworthy, however, that no such ill effects were experienced during the other experiments.

It is interesting also that both A and C developed, during the first experiment, a sudden and intense lassitude about twelve hours after a total of 600 mg. of dried gland had been taken. This lassitude wore off during the next day, but it was akin to prostration and very unlike the usual kind of fatigue resulting from strenuous exertion; both A and C were qualified to notice the difference as they had done a good deal of mountaineering in Switzerland. Since A had carefully refrained from mentioning any of her subjective sensations, and since in C the same effects were produced after the same amount of dried gland, but a day later, suggestion can hardly be held responsible for the phenomenon.

Another interesting observation made by A was the development of severe gastric pain, lasting three days, after dried suprarenal had been taken on an empty stomach. This observation was made at the end of the second experiment when A was attending the annual meeting of the American Medical Association; on account of various engagements she forgot to take the dried gland after breakfast and there was no opportunity to do so till 10 p.m., June 11. The amount of food taken during a banquet at 6 p.m. had been particularly small, so that the stomach was practically empty at 10 p.m. In less than ten minutes after the capsule containing 200 mg. of dessicated suprarenal substance had been swallowed an intense, cramping pain developed in the pit of the stomach; this pain could be increased by pressure on a small area just below the xyphoid process of the sternum, whereas no tenderness could be revealed by pressure in the region of the gallbladder or the appendix and although, since A was feeling particularly well, there seemed to be no reason whatsoever for the pain apart from the ingestion of the capsule. Chocolate was eaten (nothing else was available) in the hope of improving matters by adding to the contents of the stomach, but this had the opposite result. There was no sensation of nausea. A finally went to bed but the pain remained sufficiently severe to prevent sleep for several hours. Next morning the pain seemed to have vanished, yet it proved possible for three days to cause its return by exerting some pressure on the circumscribed area just below the xyphoid process. Two explanations of this incident seem admissible; either the adrenalin content of the dessicated adrenal substance (0.5 per cent weight, or 1 mg. for each 200 mg. of total gland) produced a local constriction of the blood vessels in the gastric mucosa where the glandular substance came into contact with the wall of the stomach, thus duplicating the well known blanching of the skin during adrenalin injections in local anesthesia; or the stimulation of A's suprarenals following the ingestion of the dried gland may have caused the constriction of the gastric capillaries. The latter interpretation is supported by the experiments of Durante (1916) who found that minute, transient hemorrhages could be produced in the gastric mucosa of animals by stimulating by way of the lumbar route any of the splanchnic nerve fibers leading to the suprarenals, with the exception of the medium splanchnic nerve of the left suprarenal; stimulation of the latter gave rise to histologic changes in the spleen and to the formation of typical, permanent gastric ulcers. It seems probable that one or more minute hemorrhagic areas were produced in the gastric mucosa of A, since three days were needed for the complete disappearance of gastric pain on pressure. Recently two of the patients with Addison's disease, whose blood findings have been given, volunteered the information, that the "pills" which they were getting, namely capsules containing total dried suprarenal, "gave them a pain in their stomach unless taken immediately after a meal".

The diagram of the blood constituents of A during 1919 (Fig. 28) offers several points of interest in connection with the experimental ingestion of dessicated suprarenal substance. Each of the three "suprarenal experiments" is indicated on the diagram by a hatched block, and it will be recalled that 1,200 mg. of dried gland was taken during the first two experiments (May 27 to 31 and June 5 to 11), whereas 2,000 mg. was used during the third experiment (July 24 to August 1). The small solid black block in the diagram represents the experimental ingestion of 1 mg. thyroxin (August 15), and the hatched block next to it stands for another 200 mg. of dessicated suprarenal taken August 24 to combat the lassitude on waking, which, as had been observed during the three experiments, seemed to be counteracted by the use of dried gland. Both A and C had noticed that they felt "slept-out" while taking suprarenal substance, whereas for some time previously the process of "waking up" in the morning had resembled the struggles of a fly, endeavoring to extricate itself after falling into a dish of honey. It is possible that this intense morning drowsiness in A and C, who are both by nature early risers, was the initial manifestation of poisoning by the fumes of the defective furnace, although the bad condition of the furnace was only discovered at the end of October.

Comparison of the left half of Figure 28, presenting the findings during the first seven months of 1919, with the right half which includes observations from the end of July to the end of December, shows distinct changes in the behavior of the blood constituents. These changes may be summarised under the following seven headings:

1. The curves of the total leukocyte counts and of the blood cholesterol tend to run in opposite directions, while the blood sugar and the cholesterol curves tend to run parallel from January to the end of July, 1919; but

the trend of the curves becomes less constant and there is a tendency in cholesterol and leukocyte curves to run parallel, while sugar and cholesterol run inversely during August, September, and October, the original relation of the curves reappearing towards the end of the year, when A was apparently "getting over" the effects of the furnace fumes in her house, which effect had incapacitated her from work from the middle of November to the end of December.

2. Very high leukocyte counts, up to 22,000, became prevalent shortly after the first "suprarenal experiment".

3. A definite rise of the Bloor I (saponified) cholesterol values becomes noticeable following the second "suprarenal experiment" and reaches its maximum (175 mg.) at the end of the third experiment, August 5; after this date the cholesterol values begin to drop again and they return to the normal level towards the end of the year.

4. There is a simultaneous drop in the total leukocytes and in the blood cholesterol following the experimental ingestion of 1 mg. thyroxin, August 15, and a similar drop but followed by a subsequent increase of both leukocytes and cholesterol after ingestion of 700 mg. of total dessicated suprarenal, August 24.

5. The blood sugar curve shows a tendency towards a higher level during the "suprarenal experiments", as may be seen in the entries of June 12, July 31, August 22, and September 25, although the sugar values are within normal range. The inverse relation of the sugar and the cholesterol curves is most marked September 25. There is a steady decline of the blood sugar values from the end of September on, the subnormal value of 0.04 gm. being reached November 6. Since this subnormal, lowest value was found but a few days after A had been exposed to a considerable concentration of carbon monoxid in the basement of her house, while trying to locate the defects of her furnace, and since similar subnormal values occurred on the same date in the blood of D (Fig. 40), who assisted A in locating the defects of the furnace, and in the blood of F (Fig. 42) and of C (Fig. 39)

following their exposure to carbon monoxid, the deduction seems warranted that the abnormally low blood sugar was a manifestation of the deleterious effect of carbon monoxid on the human body.

6. The coagulation time of A's blood appears to be reduced by the ingestion of total dessicated suprarenal: its minimum, four minutes, is reached July 29 towards the end of the third experiment. The tests were made with Bogg's coagulometer and the observations were carried on until November 20; they are represented in the diagram (Fig. 28) by the double line C.T. Although there may be certain objections to the use of the Bogg instrument the comparative data thus obtained are of interest, for in none of the subsequent observations as short a coagulation time was found as on July 29 and the longest coagulation time was nine minutes. The findings, moreover, are in accord with all other observations on the increased coagulability of the blood produced by adrenalin and it should be borne in mind that the 2,000 mg. of total dried gland, taken between July 24 and August 1, contained no less than 10 mg. adrenalin.

7. There is a striking increase in the number of cholesterol tests with subnormal split cholesterol values during the last five months of 1919. Whereas only one test in nineteen contains a subnormal amount of split cholesterol between January 31 and July 29, no less than four tests out of twenty show subnormal split cholesterol values between July 29 and December 19: expressed in terms of percentage this increase of the number of tests with too little split cholesterol equals a rise from 5 to 20 per cent. It is further noteworthy that the first of the series of subnormal split cholesterol values occurs in the determination of July 31, that is towards the end of the third "suprarenal experiment" when 10 mg. of adrenalin had been ingested in the total amount of dried gland used during the experiment. This finding is in harmony with the observations made three years later on the reduction of the split cholesterol values in the blood of patients with Addison's disease during administration of adrenalin (pages 203-205). It seems possible that the reduction of the split cholesterol values both in A and

in the patients with Addisonia is a manifestation of a temporary fatigue of the suprarenals following stimulation. The patients derived benefit from the treatment in the long run, and A's general health does not seem to have been affected by her experiments, but the work of Stewart and Rogoff proves that the body works with infinitesimal amounts of epinephrin; the total epinephrin output of an adult weighing 154 pounds does not exceed 20.16 mg., that is, less than 1/3 gr. (Ludon). The absence of split cholesterol in the blood of double adrenalectomized dogs, moreover, is a fact which lends support to the conception that temporary suprarenal weariness might also diminish suprarenal activity and thus reduce the capacity of the body for "splitting" its cholesterol.

The evidence supplied by the findings in Figure 28 does not answer the questions: Are the changes in A's blood during the latter part of 1919 to be ascribed to the ingestion of desiccated suprarenal, or to prolonged exposure to carbon monoxid containing furnace fumes, or to the combined action of both of these factors? Any attempt to answer these questions definitely seems doomed to failure, because two widely divergent reactions in A are conceivable, while neither of them is amenable to proof. The ingestion of dried suprarenal may have helped A to overcome more readily the deleterious effects of exposure to carbon monoxid, thus rendering the chemical changes in the blood less marked than they would otherwise have been. Or, since increased activity tends to produce fatigue, the stimulation of suprarenal activity by the ingestion of dried gland may have rendered A's suprarenals more susceptible to the strain put on them during A's exposure to "toxic" combustion products. The first interpretation is supported by the well known, beneficial effects of suprarenal medication in Addisonia and by A's complete recovery from the effects of prolonged exposure to carbon monoxid, although these effects were severe enough to incapacitate A for work during several weeks in spite of her unusually strong physique; but the second interpretation is also defensible on the following grounds. The cardinal symptoms of Addison's disease are admittedly: muscular weakness, nausea, headaches, circulatory irregularities, hypotension, fainting spells, chilliness, low blood sugar values and bronzing of the skin. During the weeks of unsuspected exposure to furnace fumes transient bronzing was observed not only in A, but also and in an even more marked degree in F, who had not taken dried suprarenal substance experimentally; and most of the symptoms forming part of the Addisonian syndrome occurred not only in A, but in C, D, and F as well. These facts suggest that carbon monoxid has a decidedly deleterious effect on the suprarenals; and that, if the symptoms of Addison's disease are connected with total or partial destruction of the suprarenal glands, the symptoms of chronic carbon monoxid poisoning may be referable, in part at least, to a transient and reparable depression of suprarenal function. Sézary (1921) has pointed out that changes in the color of the skin simulating those in Addisonia have been found in pathologic conditions, in which necropsies failed to reveal any macroscopic or microscopic changes in the suprarenal glands. Histologic integrity, however, does not necessarily guarantee unimpaired physiologic function of tissues; and the similarity of the symptoms produced by prolonged exposure to carbon monoxid to the whole syndrome of Addison's disease is sufficiently close to be worth considering; because of the ubiquity of carbon monoxid in modern civilization which has been discussed in detail in Chapter XI.

The fourth observation concerning the influence of suprarenal activity on the amount of cholesterol split products in the blood was made, March, 1921, during experimental alimentary glucose tolerance tests by A, C, and F; this observation appears to have some bearing on the moot question of the interaction between the suprarenals and the pancreas.

One glucose tolerance test was done by C (Fig. 39) and two tests were made at one week's interval by A and by F (Fig. 62). The technic recommended by Hamman and Hirschman (1917) was followed in all the tests: blood samples were taken before the ingestion of 100 gm. of glucose and at intervals of thirty, sixty, ninety and one hundred fifty minutes after ingestion. The blood sugar and the blood cholesterol values were determined on the same sample in every instance. Benedict's method was used for the sugar determinations, and the cholesterol tests were done according to Bloor's methods, I (saponified) and II (unsaponified). Samples of urine were taken at the same intervals as the blood samples and tested for sugar according to the qualitative and the quantitative method of Benedict. The blood sugar curves of the three experimentors appeared to be absolutely normal; urinalysis, as was to be expected, failed to reveal the slightest trace of sugar in any of the specimens, but the blood cholesterol determinations furnished some interesting data.

It has recently been pointed out by Beeler, Bryan, Cathcart and Fitz (1922) that Hamman and Hirschman's glucose tolerance test does not make any allowance for the different rates of glucose absorption in the stomachs of different persons. It was decided, therefore, to check the previous findings in A, C, and F by the new method of Beeler, Bryan, Cathcart and Fitz. This method consists in removing the ingested glucose at the end of a given time by means of a Rehfuss stomach tube and in establishing the rate of absorption through the amount of glucose thus recovered. Attempts to do a glucose tolerance test according to the new method on A (whose cholesterol values were particularly interesting) failed because of an unforeseen difficulty: when swallowing the Rehfuss tube, A somehow managed consistently to shift it from her pharynx into her larynx, whence it had to be removed in a hurry. Several attempts with the "large" tube gave the same results, notwithstanding the fact that the "tubing" was done by the head of the gastric laboratory, an expert in these matters, who finally declined to take any further chances by continuing the attempts. Although the factor of glucose absorption is doubtless an important one in glucose tolerance tests, the use of the old technic does not appear to have vitiated the findings in A, C and F to any great extent; for the diagrams (Figs. 39 and 62) show sugar curves which correspond closely to those usually obtained in normal persons, as there is "an increase of the blood sugar concentration which reaches its maximum in thirty minutes, returns to normal in sixty minutes and remains at normal or below normal for several hours

minutes; whereas the blood sugar of A rose from 0.100 gm. to 0.150 gm. in thirty minutes, but returned to and remained at 0.110 gm. till the end of two and one-half

afterwards" (Beeler, Bryan, Cathcart and Fitz).

Findings of interest in the glucose tolerance tests of A, C, and F follow. The diagram of C (Fig. 39) shows a consistently inverse relation between the cholesterol and the sugar curves, a high normal leukocyte count (10,500) before ingestion of the glucose and large amounts of split cholesterol in all the determinations. Whether the fact that C's blood sugar values remained unaltered at their initial value of 0.130 gm. for ninety minutes, dropped to 0.090 gm. and rose to 0.100 only at the end of one hundred fifty minutes, should be considered evidence of a slow rate of glucose absorption is difficult to decide; it is possible that the blood sugar increased later, but two and one half hours are supposed to be a sufficiently long period for glucose tolerance tests as a rule.

In the diagrams of F and A (Fig. 62) the relation of the blood cholesterol and the blood sugar curves is much less regular than in the diagram of C, as a tendency to parallelisms may be observed, especially during the second experiment. The total leukocyte counts, taken before ingestion of the glucose, show a low normal range for F (6,400 to 8,400) and a high range for A (10,900 to 13,500). During the first experiment the blood sugar of F remained, following the ingestion of the glucose, at its initial value of 0.110 gm. for ninety minutes, when it fell to 0.090 gm. to rise again to 0.100 gm. at the end of one hundred fifty minutes; whereas the blood sugar of A rose from 0.100 gm. to 0.150 gm. in thirty minutes, but returned to and remained at 0.110 gm. till the end of two and one-half hours. During the second experiment the blood sugar curves of F and A may be called normal as they show a definite rise (which is higher for A than for F) at the end of thirty minutes and a return to normal values during the subsequent determinations.

The behavior of the split cholesterol in F and A during the sugar tolerance tests constitutes the most interesting feature of these experiments. The diagrams of F show a consistent drop of the split cholesterol to a subnormal (11 mg.) and to the lowest normal (17 mg.) value in both experiments in the determination made at the end of ninety minutes, although large amounts of split cholesterol occur in all the other determinations. In the case of A a total lack of cholesterol split cholesterol occurs at the end of sixty minutes in both experiments, which were made at one week's interval; but there is plenty of split cholesterol at the end of ninety minutes, although in the second experiment the amount of split cholesterol is subnormal again at the end of two and one-half hours.

The transient total lack of cholesterol split products in the blood of A and the marked reduction of the split cholesterol of F during the sugar tolerance tests do not seem to be accidental findings for the following reasons: So far, in all our cholesterol determinations, which include the study of more than 3,000 individual blood samples, a total lack of cholesterol split products in the blood has been observed only in pathologic conditions, and in determinations which could not be affected by the digestive process because the blood samples were always taken before breakfast; nor has such a lack of split cholesterol been found in numerous studies on digestion, including a number of experiments on A and F in which the technic of the glucose tolerance test was followed, while the food used was not glucose but an ordinary breakfast composed of bacon and eggs, or cold ham, bread and butter and tea or coffee with sugar and cream.

A total lack of split cholesterol during the postdigestive period was found, however: (1) in 56 per cent of the patients suffering from malignant conditions, which were not complicated by ulceration or severe hemorrhages and before the use of therapeutic measures such as operations or radiotherapy; (2) in three patients whose condition contained, so to speak, an element of malignancy, namely one case of scleroderma, one case of a persistent eosinophilia of no less than 80 to 93 per cent in which a definite diagnosis proved impossible and one case of fatal liver abscess in which histologic examination of the suppurating area of the liver showed a picture suspiciously like carcinoma, although extensive cell destruction and the very poor staining qualities of the tissue forbade definite conclusions*; (3) in two patients with subnormal metabolic rates, one of whom had the peculiar pallor which often accompanies malignancy, although clinical evidence was lacking at the time, while the other had an advanced degree of myxedema*; (4) in one patient with Addison's disease, some ten hours after hypodermic injection of 1 c.c. of a solution of adrenalin (1:1000); and (5) in three double adrenalectomized dogs.

The last two of the foregoing observations seem to point definitely to the suprarenals as concerned in the regulation of the amount of split cholesterol in the blood, while the findings in the blood of A and of F during the glucose tolerance tests as well as the marked reduction of the split cholesterol in the blood of A during her experimental oatmeal diet (pages 17 and 18 Part II) recall the controversy about the interaction of the suprarenals and the pancreas. Pemberton and Sweet (1908-1912) demonstrated that the injection of epinephrin decreases or inhibits the flow of pancreatic juice and that removal of the adrenals increases pancreatic secretion. Mann and Drips (1915) state that "In general our results corroborated those of Pemberton and Sweet", namely in observations made on the flow of the pancreatic juice in normal, anesthetised animals for eight to sixteen hours after "various procedures to the adrenal" (Group I). But they also found that the increase of the pancreatic juice after double adrenalectomy in anesthetised animals "is insignificant as compared to the flow during the process of digestion"; after double adrenalectomy the flow "rarely exceeded 0.05 c.c. in a quarter of an hour, while "during the digestive period the secretion was as much as 1 c.c. per minute", in unanesthetised animals of approximately the same size. Mann and Drips conclude from these and from numerous other experiments that the changes found in the pancreas after removal of the suprarenals are the result of changes in the blood pressure and that they furnish no evidence of any specific relation between suprarenals and pancreas. "Sülzer saw glycosuria disappear after ablation of both adrenals. He also found that adrenalin glycosuria is prevented

* Only one blood cholesterol determination could be obtained in these patients.

by pancreatic extract and even by pancreatic juice" (Warthin, 1922), an observation which recalls the recent therapeutic results obtained in diabetes with the insulin of Banting, Collip, Macleod, and Noble (1922). Hoskins (1922) says: "For a time much stress was laid on the fact that fresh pancreatic pulp rapidly causes the destruction of epinephrin. Largely upon this fact an elaborate theory of pancreatic suprarenal antagonism was founded. The destruction of epinephrin by pancreatic material seems definitely to be ascribed to its alkalinity". Warthin (1922) summarizes his review of "the mass of experimental work" done on the pancreas with the words: "That the pancreas is a gland of internal secretion is now universally accepted as a firmly established fact of physiology and pathology. Of the nature of this internal secretion we know nothing but that it is essential to carbohydrate metabolism . . . and is antagonistic to the secretion of the adrenal medulla".

In the midst of these conflicting opinions two observations stand out which seem to have a bearing on my findings concerning the total lack of split cholesterol in the blood of dogs deprived of both suprarenals and in the blood of A sixty minutes after ingestion of 100 gm. of glucose. These two observations are the prevention of adrenalin glycosuria by the use of pancreatic extract reported by Zülzer and the great increase of the flow of pancreatic secretion observed during the digestive process by Mann and Drips; and the connection between these findings and the behavior of the split cholesterol would seem to be the following.

It will be admitted that the ingestion of 100 gm. of glucose is likely to cause an increased activity on the part of the pancreas, and that the maximal increase of pancreatic activity is likely also to occur from thirty to ninety minutes after the ingestion of the glucose. The total lack of split cholesterol in the blood of A occurred at the end of sixty minutes in two glucose tolerance tests made at one week's interval; a marked reduction of the split cholesterol was found in the blood of F at the end of ninety minutes under the same experimental conditions; the difference in time, sixty and ninety minutes is probably connected with the rate of absorption of the glucose. The total lack of split cholesterol in the blood of the three dogs became manifest after the second suprarenal had been removed, and it did not occur in liverless dogs even when the latter were moribund. In view of these findings the deduction seems admissible that the suprarenals were forced to "take a back seat" so to speak, during the height of pancreatic activity; for at the height of glucose digestion the cholesterol split products in the blood were reduced to the level which is found when the suprarenals are absent or their activity is temporarily depressed.*

The foregoing findings point to an interesting connection between many independent observations concerning the anomalies of both cholesterol and sugar metabolism in malignancy; they suggest a host of problems, all dealing with the influence of metabolic disturbances on malignant growth; problems of which the solution may prove to be of vital importance to the sufferers of malignant disease. The high, prolonged sugar curves, commonly found in diabetes, but also observed by Rohdenburg, Bernard and Krehbiel (1919) in patients with cancer and studied in detail by Friedenwald and Grove (1920); the lack of adrenalin hyperglycemia in animals with spontaneous tumors reported by Rohdenburg (1920); the tendency to parallelism between the cholesterol and the sugar curves when the body mechanism is feeling the effects of extra strain resulting from divers causes; the total lack of split cholesterol in more than one-half of the patients with malignancy before treatment, in double adrenalectomized dogs and in sugar tolerance tests, and many other observations appear to be like the scattered links of a chain which may become serviceable when the necessary joining and riveting has been done by many workers.

But the words of Hoskins (1922) should be recalled in this connection: "Whether, as is often assumed, all the endocrine organs stand in intimate functional relationship to each other, has by no means been demonstrated.

* The fact that large amounts of split cholesterol were found in the blood in a case of diabetes appears to support this deduction, but the findings are too few as yet to be of value, and the complex relation of cholesterol and fat metabolism will also have to be considered.

The facile theorizing that has been indulged in by numerous uncritical writers is not justified. . .. A great many more careful investigations are needed. The problem is one of the most difficult in all biology. In its solution the demands of adequate technique, extensive data and rigid logic are inescapable."

While data presented in this chapter and in previous ones can hardly be called scanty, as they are based on the study of more than 3000 blood samples and on observations made during a period of more than seven years, much of the work has been handicapped inevitably by the force of circumstances. Although every effort has been made to meet the demands of both rigid logic and that self-criticism which is the _sine qua non_ of all investigation; and although attempts have been made to correlate all observations with the work of others, a constant watch being kept for elements conducive to technical errors, the findings themselves are little more than fragmentary. So far, however, most of the subjects which have been discussed have been considered matters of importance by a relatively small number of investigators, and the work of many is needed. The historical development of the biochemical conception of malignant growth; the relation of the blood cholesterol to the problems of malignancy and to many other problems in medicine; the value of serial blood cholesterol determinations by Bloor's two methods for prolonged periods; the importance of the diet in malignant disease and the changes in the blood connected with dietary measures in malignancy; the relation of the combustion products of fuel to the cancer problem and the biochemical basis of this relationship; the value of correlating observations on the behavior of certain blood constituents with other findings; the significance of the cholesterol split products in the blood and the vistas which the study of these products offers with regard to the interaction of certain endocrine glands; all of these have received but little attention or none at all. Yet each of these subjects represents a fruitful field of research and innumerable problems, all connected with the great problem of malignant disease, which is a matter of vital importance, not only to investigators but to the whole of humanity.

The two aspects of the biochemical conception of malignancy

The biochemical conception of malignant growth embodies simultaneously the most pessimistic and the most hopeful view of the cancer problem; it resembles the old Roman deity Janus, the double-faced, who represented to his worshippers both War and Peace.

If a biochemical disbalance in the organism is the fundamental etiologic factor in malignant growth, then the progress of civilisation would seem inseparably linked with the occurrence of malignancy and the prevention or control of cancer would appear to be only Eutopian dreams. Cancer is by no means a new disease; it is mentioned in the earliest records of history; it is probable that it was met with even in prehistoric times. Factors capable of disturbing the biochemical balance in the body through damage to some part of the chemical machinery were no more lacking in the Stone Age than they are today: chronic suppuration resulting from a wound inflicted by a primitive weapon or by the fangs of some prehistoric animal constituted, for example, as much of a drain on the suprarenal glands and was just as effective in putting other organs out of commission as empyemas or chronic ulcerations in modern days. Civilization, however, has multiplied _ad infinitum_ the means by which the chemical balance within the body may be disturbed; and it is immaterial, so far as the end results are concerned, whether the body's chemical mechanism is initially impaired by the toxic products of chronic suppuration, by exposure to extraneous, injurious chemical agents or by the ingestion of adulterated and inadequate food. Since it is as impossible to stem the march of civilization as it was futile to resist the advance of Juggernaut's car, the mangled victims of Progress are likely to exceed in numbers those attributed to the passage of the cruel Indian idol. This is the pessimistic and most depressing aspect of the biochemical conception of malignancy.

Fortunately, the biochemical conception has another, consoling and cheering aspect; because of the prospects which it holds out to the victims of malignant growth. The modern treatment of pancreatic diabetes is helping thousands of patients, through the achievements of chemical investigation, to live in comparative comfort, to enjoy fair health and an unimpaired capacity for work in spite of a damaged pancreas. The broken cogwheels of the body engine cannot be replaced, although by careful management they can be induced to accomplish their daily tasks to the satisfaction of their owner. These are the prospects which the biochemical conception offers to the victim of malignant growth.

The victory over malignant disease will remain, in all probability, the relative gain of a drawn battle, rather than the decisive and final rout of the enemy: the recurrence of malignancy as long as twenty-eight years after the elimination of its initial manifestations testifies to the truth of this contention. The problem which the biochemical conception gives the physician to solve with regard to the welfare of his patients recalls an old idiom of the Netherlands in which tasks requiring constant attention are compared to "keeping a ten cent piece rolling on its thin edge": rough spots in the surface over which the small coin travels must be expected to upset its labile equilibrium; the many injurious agents found in civilised life are likely to tax the chemical stability of the body in which malignant growth developed; they should be considered and guarded against. Yet the fact that no less than 100 patients with inoperable, "hopeless" malignant conditions and a reliable diagnosis (Rohdenburg) became "clinically well" is conclusive evidence that the human body can recover and maintain its balance of health to a surprising and unexpected extent. If a limited number of patients accomplished this feat unaided, surely many more might be able to do so with judiciously applied assistance, even though the type of help that was needed might differ in given cases; for every patient will ever be an individual problem. How the patients mentioned by Rohdenburg got well is for modern cancer research to discover. If, as the biochemical conception of malignancy assumes, the cancer problem is a chemical problem, it will be solved by chemical investigation, for chemistry today is equipped with instruments and methods as it never was before. The discovery of insulin furnishes a new basis for these expectations. This is one of the cheering aspects of the biochemical conception of malignancy.

The variable results of surgery, of radiotherapy and of other methods of treatment in cancer are well known. Therapeutic measures which proved to be of the greatest benefit to a great number of patients have failed to bring any relief to others. The biochemical conception of malignancy throws a ray of light on the problem of these triumphs and failures; it calls attention to the fact that the relative integrity of the chemical laboratories in the body of a given patient is the fundamental factor in the patient's response to treatment, while the far-reaching destruction of the chemical machinery in another patient was the fundamental cause of failure; it also emphasises that new means may be found which will insure new triumphs as has been done in the treatment of diabetes. Perhaps no single, specific method of treatment will be discovered, for the diverse types of malignant growths make it seem improbable that there should be a single cause of malignancy. Yet the biochemical conception of malignant growth holds out hope that chemical investigations will show the way and provide the means by which the individual needs of the individual sufferer can be recognised and remedied; this is another cheering aspect of the biochemical conception of malignancy.

Summary and conclusions

1. The history of cancer research shows that the formerly much derided biochemical conception of malignant growth has not only survived through twenty-four centuries, but that it is gaining ground today because instruments and methods for chemical investigations are available.

2. In the regulation of the chemical composition of the blood the functional activity of the glands of internal secretion plays a prominent part.

3. The chemical composition of the blood must affect the growth, the differentiation and the rate of proliferation of the cells of the body, because the life of the cell depends on its blood supply. Chemical factors must therefore be among the primary factors which initiate and further the malignant proliferation of cells. There is ample evidence that the individual chemistry of the host determines the rate of growth of the tumor. This has been demonstrated experimentally by the fate of tumor grafts in animals and clinically by the occurrence and recurrence of tumors in so-called predisposed persons.

4. Recognition of the foregoing indisputable facts leads, logically, to the conclusion that the chemical conditions which make an animal or a human body well suited for the development of tumors, should receive the first and foremost consideration in all investigations intended to solve the problems of malignant growth.

5. It will be granted that the chemical conditions in the body are primarily the result of metabolic processes, and that normal metabolic processes furnishing normal chemical conditions are not likely to produce malignant cell proliferation, representing an impairment of health.

6. It does not seem warranted to assume that there is only one cause of malignancy; because many divers factors, such as the hereditary transmission of inadequate organs, ill-balanced diets, bacterial infections and exposure to injurious chemical agents, are each and all capable of reducing the functional efficiency of one or more of the endocrine glands, thus leading to abnormal meta-

bolic and chemical conditions within the body. And it should be recalled that the body works with incredibly small amounts of its important chemical constituents.

7. Admission of the foregoing premises, however, transfers the problems of malignant growth from the domain of histology to the realms of biologic chemistry; it reduces the importance of the structural imperfections of the cell unit and emphasizes the importance of the chemical conditions under which the cell unit is forced to exist; it compels us to look on malignant neoplasia as the result of abnormal chemical conditions, furnished by abnormal metabolic processes; it discredits the conception of cancer as a local disease; it vindicates the conception of malignant growth as a disease of metabolic origin.

8. Determinations of the blood cholesterol are of special value in the study of malignant growth because cholesterol is intimately associated with the multiplication of cells. The mechanism by which cholesterol furthers cell proliferation has not yet been fully explained, but the following facts are evidence that cholesterol plays an important part in cell formation and cell division; (a) during the process of hatching, the cholesterol content of the egg-yolk is utilized for the formation of the cells which constitute the body of the chick embryo, (b) during gestation, both in human beings and in animals, the increase of the cholesterol content of the mother's blood is most marked at the time when the growth of the fetus is the most rapid; and, under normal conditions, the mother's blood cholesterol returns to its normal level after the offspring has been born, (c) addition of cholesterol to the culture medium accelerates the rate of cell division in paramecium from three to five times, (d) intravenous injections of cholesterol in tumor-bearing rats have been found to double the rate of growth of the tumor grafts, (e) disturbances of cholesterol metabolism occur in malignant conditions, notably in cancer; they are characterized by an increase of the blood cholesterol and a reduction of the cholesterol split products in the blood, (f) cholesterol metabolism improves under radium treatment (of which the beneficial effects need no comment) when the patient is capable of responding to treatment,

(g) cholesterol metabolism is influenced by the basal metabolic rate as shown by the inverse relation between the blood cholesterol values and the metabolic rate in myxedema and in hyperthyroidism, and (h) disease in which high blood values are common and persistent are often associated with malignant conditions. But the test for cholesterol in the blood is not a diagnostic test for malignancy; it is merely a clinical test capable of giving valuable information about the way in which the body is handling its cholesterol.

9. Cellular pathology, which looked on cell morphology as the key to the cancer problem, has neither revealed the cause, nor found the cure for cancer, but the patient labors of the pathologist have paved the way for the future work of the chemist.

10. Chemical analyses are the logical mode of attack in the study of any disease caused by chemical disturbances in the body. The progress of modern chemistry warrants that the more general admission of the biochemical conception of malignant growth and researches along chemical lines will alleviate the sufferings and better the prospects of the victims of malignant disease, because scientific achievements have always been controlled by the technical facilities which investigators had at their command. Biochemical investigation will solve the cancer problem.

BIBLIOGRAPHY

1. Autenreith and Funk: Quoted by Bailey.

2. Bailey, H.: Pathological metabolism in pregnancy. In: Barker, L.F.: Endocrinology and Metabolism. New York, Appleton, 1922, iv, 835-859.

3. Banting, F.G., Best, C.H., Collip, J.B., Macleod, J.J.R. and Noble, E.C.: The effect of pancreatic extract (insulin) on normal rabbits. Am. Jour. Physiol., 1922, lxii, 162-176.

4. Barker, L.F.: Clinical syndromes due to disorders of the parathyroid glands. Endocrinology and Metabolism, New York, Appleton, 1922, i, 577-703.

5. Bates: Quoted by Sajous, 1919.

6. Beck, H.G.: Dystrophia adiposogenitalis. In: Barker, L.F.: Endocrinology and Metabolism. New York, Appleton, 1922, i, 922.

7. Béclère: Les rayons de Röntgen dans le traitement des tumeurs hypophysaires du gigantisme et de l'acromégalie. Jour. de radiol. et d'électrol., 1914, i, 138-145.

8. Beeler, Carol; Bryan, A.W.; Cathcart, E.P. and Fitz, R.: An improved alimentary glucose tolerance test. Jour. Metabolic Res., 1922, i, 549-560.

9. Benedict, S.R.: A modification of the Lewis-Benedict method for the determination of sugar in the blood. Jour. Biol. Chem., 1918, xxxiv, 203-207.

10. Benedict, S.R. and Lewis, R.C.: The sugar content of the blood in cancer. Med. Rec., 1914, lxxxvi, 650-651.

11. Boruttau: Quoted by Crawford.

12. Bowing, H.H.: Topical applications of radium. Am. Jour. Roentgenol., 1920, vii, 582-583.

13. Bowing, H.H.: Radium and x-ray therapy in inoperable carcinoma of the cervix. Med. Herald and Electro-Therapist, 1921, xl, 43-46.

14. Bullock, F.D. and Rohdenburg, G.L.: Splenectomy exerts no appreciable influence upon immunity against transplanted tumors. Jour. Cancer Res., 1917, ii, 465-469.

15. Cannon, W.B.: The emergency function of the suprarenal medulla. In: Barker, L.F.: Endocrinology and Metabolism. New York, Appleton, 1922, ii, 171-185.

16. Cohoe, B.A.: Clinical syndromes due to suprarenal diseases. Addison's disease. In: Barker, L.F.: Endocrinology and Metabolism. New York, Appleton, 1922, ii, 277-311.

17. Cohoe, B.A.: Clinical syndromes due to suprarenal diseases. Hypoadrenia. In: Barker, L.F.: Endocrinology and Metabolism. New York, Appleton, 1922, ii, 313-326.

18. Cramer: Quoted by Crawford.

19. Crawford, A.C.: Chemistry of the suprarenal glands. In: Barker, L.F.: Endocrinology and Metabolism. New York, Appleton, 1922, ii,77-98.

20. Denis, W.: Cholesterol in human blood under pathological conditions. Jour. Biol. Chem., 1917, xxix, 93-110.

21. Dibbolt: Quoted by McCrudden.

22. Dieffenbach, W.H.: Osteomalacia: Is it a rare or rather common disease? Med. Rec., 1920, xcvii, 995-997.

23. Durante, L.: The trophic element in the origin of gastric ulcer. Surg., Gynec. and Obst., 1916, xxii, 399-406.

24. Editorial: L'intoxication par l'oxyde de carbonne. Presse méd., 1922, xxx, 1427-1428.

25. Edsall: Quoted by Hurwitz.

26. Evans, H.M.: The rhythm of gonodal function with special reference to the relations between uterus and ovary. In:Barker, L.F.: Endocrinology and Metabolism. New York, Appleton, 1922, ii, 579-599.

27. Finzi, O.: Über Veränderungen der Magenschleimhaut bei Tieren nach Nebennierenexstirpation und über experimentall erzeugte Magengeschwüre. Arch. f. path. Anat., 1913, ccxiv, 413-432.

28. Folin, O. and Wu, H.I.: A system of blood analysis. Jour. Biol. Chem., 1919, xxxviii, 81-110.

29. Freund, E. and Kaminer, G.: Ueber karzinolytische organische Säuren. Wien. klin. Wchnschr., 1919, xxxii, 1105-1107.

30. Frey, W. and Hagemann, E.: Die Brauchbarkeit der Adrenalinlymphocytose zur Funktionsprufung der Milz. Klinisches und experimentelles Beweismaterial. Ztschr. f. klin. Med., 1921, xcii, 450-465.

31. Friedenwald, J. and Grove, G.H.: The blood-sugar tolerance test as an aid in the diagnosis of gastro-intestinal cancer. Am. Jour. Med. Sc., 1920, clx, 313-323.

32. Glaevecke: Quoted by Novak.

33. Grafe, E.: Die Steigerung des Stoffwechsels bei chronischer Leukämie und ihre Ursachen. Deutsch. Arch. f. klin. Med., 1911, cii, 406-430.

34. Graves: Quoted by Vincent.

35. Grawitz, E.: Klinische Pathologie des Blutes. 4 ed. Leipzig, G. Thieme, 1911, 274-276.

36. Halsey, J.T.: Organotherapy and hormonotherapy. In: Barker, L.F.: Endocrinology and metabolism. New York, Appleton, 1922, i, 122.

37. Hamman, L. and Hirschman, I.I.: Studies on blood sugar. I. Alimentary hyperglycemia and glycosuria as a test of sugar tolerance. Arch. Int. Med., 1917, xx, 761-808.

38. Hartman, F.A.: The general pharmacology and toxicology of the suprarenal glands. In: Barker, L.F.: Endocrinology and Metabolism. New York, Appleton, 1922, ii, 237-255.

39. Hawk, P.B.: Practical physiological chemistry. 6 ed. Philadelphia, Blackstone and Son, 1919, 276.

40. Henderson, Y., Haggard, H.W. and Scott, S.: The treatment of carbon monoxid asphyxia by means of oxygen + CO_2 inhalation. Jour. Am. Med. Assn., 1922, lxxix, 1137-1145.

41. Henning, B.H.: The lipoids of the blood in tuberculosis. Jour. Biol. Chem., 1922, liii, 167-170.

42. Hower, E.E.: Some functions of the suprarenal glands. Brit. Med. Jour., 1922, i, 138-139.

43. Hoskins, R.G.: Introduction: Endocrinology and Metabolism. New York, Appleton, 1922, i, 42.

44. Hoskins, R.G.: Relation of the suprarenal glands to the circulation. In: Endocrinology and Metabolism. New York, Appleton, 1922, ii, 187-234.

45. Hoskins, R.G.: Interrelation of the endocrin organs. Endocrinology and Metabolism. New York, Appleton, 1922, ii, 919-931.

46. Hoskins and Gunning: Quoted by Hoskins.

47. Hurwitz, S.H.: Pathological metabolism of the blood and blood-forming organs. In: Barker, L.F.: Endocrinology and Metabolism. New York, Appleton, 1922, iv, 553-605.

48. Iscovesco, H.: Les lipoides. Presse méd., 1922, xxx, 653-655.

49. Johanssen: Quoted by Murlin.

50. Johnstone, E.M.: Quoted by Mann.

51. Joslin, E.P.: The treatment of diabetes mellitus. 2 ed. Philadelphia, Lea and Febiger, 1917, 559.

52. Kikkoji: Quoted by Hurwitz.

53. Killian, J.A. and Kast, L.: A study of significant chemical changes in the blood coincident with malignant tumors. Arch. Int. Med., 1921, xxviii, 813-826.

54. de Kruif, P.H.: Our medicine men. New York, The Century Co., 1922, 237.

55. Lewin, L.: Die Kohlenoxydvergiftung. Berlin, J. Springer, 1920, 370.

56. Lifschütz, I.: Die Abbauprodukte des Cholesterins in den tierischen Organen (Begleitstoffe der Blutcholesterins). Ztschr. f. physiol. Chem., 1921, cxvii, 201-211.

57. Lifschütz: Quoted by Luden.

58. Lippmann: Quoted by Sajous, 1919.

59. Luden, Georgine: The cytology of normal goat's blood. Internat. Assn. Med. Mus., 1916, vi, 73-92.

60. Luden, Georgine: Observations on cholesterin retention as a factor in cell proliferation. Jour. Lab. and Clin. Med., 1915-1916, i, 662-676.

61. Luden, Georgine: Observations on the changes in the cholesterol content of the blood of goats. Jour. Biol. Chem., 1916, xxvii, 273-295.

62. Luden, Georgine: Studies on cholesterol. III. The influence of bile derivatives in Bloor's cholesterol determinations (Preliminary report). Jour. Biol. Chem., 1917, xxix, 463-474. Also: Jour. Lab. and Clin. Med., 1917, iii, 93-109.

63. Luden, Georgine: Studies on cholesterol. IV. Experiments concerning the relation of the diet, the blood cholesterol and the "lymphoid defence". Jour. Lab. and Clin. Med., 1917, iii, 141-174.

64. Luden, Georgine: Studies on cholesterol. V. The blood cholesterol in malignant disease and the effect of radium on the blood cholesterol. Jour. Lab. and Clin. Med., 1918, iv, 849-864.

65. Luden, Georgine: Chronic carbon monoxid poisoning, its immediate and subsequent manifestations. Modern Med., 1921, iii, 102-106; 167-170.

66. McCallum, W.F.: A text-book of pathology. 2 ed. Philadelphia, Saunders, 1920, 1155 pp.

67. McCombs, R.S.: Clinical manifestations of illuminating gas poisoning. Am. Jour. Med. Sc., 1912, cxliv, 577-584.

68. McCrudden, F.H.: Metabolism in disease of the bones and joints. In: Barker, L.F.: Endocrinology and Metabolism. New York, Appleton, 1922, iv, 733-778.

69. Magnus-Levy: Quoted by Murlin.

70. Mann, F.C.: A further study of the gastric ulcers following adrenalectomy. Jour. Exper. Med., 1916, xxiv, 329-332.

71. Mann, F.C.: The spleen as an endocrin organ. In: Barker, L.F.: Endocrinology and Metabolism. New York, Appleton, 1922, ii, 663-671.

72. Mann, F.C. and Drips, Della: The relation of the adrenals to the pancreas. Arch. Int. Med., 1915, xvi, 681-692.

73. Marshall and Jolly: Quoted by Vincent.

74. Martin and Denis: Quoted by Hurwitz.

75. Mauriac, P. and Cabonat, P.: Contribution à l'étude des variations de la formule leucocytaire chez l'homme normal. Paris méd., 1921, xxxix, 407. Abstr. Jour. Am. Med. Assn., 1921, lxxvii, 72.

76. Mayo, C.H.: The surgical treatment of exophthalmos. Jour. Am. Med. Assn., 1914, lxiii, 1147-1149.

77. Millet, J.A.P. and Mueller, T.: Some phases of radium action with special reference to the hematopoietic system. Jour. Cancer Res., 1918, iii, 127-179.

78. Mohr: Quoted by Hurwitz.

79. Motzfeldt: Quoted by Cohoe.

80. Murlin, J.R.: Normal processes of energy metabolism. In: Barker, L.F.: Endocrinology and Metabolism. New York, Appleton, 1922, iii, 515-660.

81. Murphy, J.B.; Hussey, R.G.; Nakahara, W. and Strum, E.: Studies on x-ray effects. VI. Effect of the cellular reaction induced by x-rays on cancer grafts. Jour. Exper. Med., 1921, xxxiii, 299-313.

82. Murphy, J.B.; Means, J.H. and Aub, J.C.: Clinical calorimetry. XXII. The effect of roentgen-ray and radium therapy on the metabolism of a patient with lymphatic leukemia. Arch. Int. Med., 1917, xix, 890-907.

83. Murphy, J.B.; Hussey, R.G.; Strum, E. and Nakahara, W.: Effect of induced cellular reaction on the fate of cancer grafts. IV. Studies on lymphoid activity. Jour. Exper. Med., 1921, xxxiii, 315-326.

84. Murphy, J.B. and Morton, J.J.: The lymphocyte in natural and induced resistance to transplanted cancer. II. Studies in lymphoid activity. Jour. Exper. Med., 1915, xxii, 204-211.

85. Murray, G.R.: Some aspects of internal secretion in disease. Lancet, 1913, ii, 199-204.

86. Musser and Edsall: Quoted by Hurwitz.

87. Myers, V.C.: Body tissues and fluids. In: Barker, L.F.: Endocrinology and Metabolism. New York, Appleton, 1922, iii, 423-479.

88. Myers, V.C. and Fine, M.S.: The non-protein nitrogenous compounds of the blood in nephritis, with special reference to creatinine and uric acid. Jour. Biol. Chem., 1915, xx, 391-402.

89. Myers, V.C. and Killian, J.A.: Studies on animal diastases. I. The increased diastatic activity of the blood in diabetes and nephritis. Jour. Biol. Chem., 1917, xxix, 179-189.

90. Nakahara, W. and Murphy, J.B.: The lymphocyte in natural and induced resistance to transplanted cancer. VI. Histological comparison of the lymphoid tissue of naturally immune and susceptible mice. Jour. Exper. Med., 1921, xxxiii, 327-336.

91. Nakahara, W. and Murphy, J.B.: Studies on x-ray effects. X. The biological action of small doses of low frequency x-rays. Jour. Exper. Med., 1922, xxxv, 475-486.

92. Narat, J.K.: Treatment after irradiation with roentgen ray. Jour. Am. Med. Assn., 1922, lxxix, 1681-1684.

93. Neuberg, C.: Chemisches zur Carcinomfrage. I. Ueber die Wirkungsweise des Radiums bei Carcinom. Ztschr. f. Krebsforsch., 1904, ii, 171-176.

94. de Niord, R.N.; Schreiner, B.F. and de Niord, H.H.: The effect of roentgen rays on the metabolism of cancer patients. Arch. Int. Med., 1920, xxv, 32-57.

95. Novak, E.: Influence of the ovary on the development of the female generative tract. In: Barker, L.F.: Endocrinology and Metabolism. New York, Appleton, 1922, ii, 611-637.

96. Ordway, T. and Knudson, A.: Influence of roentgen rays upon metabolism. In: Barker, L.F.: Endocrinology and Metabolism. New York, Appleton, 1922, iii, 875.

97. Pemberton and Sweet: Quoted by Mann and Drips.

98. Pisani and Savare: Quoted by Bailey.

99. de Quervain, F.: Clinical surgical diagnosis for students and practitioners. 3 English ed. New York, Wm. Wood and Co., 1922, 914.

100. Quick, D.: The conservative treatment of cervical lymphatics in intra-oral carcinoma. Jour. Am. Med. Assn., 1921, lxxvii, 436-442. Abstr. Radium Therapist, 1922, i, 153-154.

101. Rohdenburg, G.L.: The glycemic reaction in its relation to transplantable malignant tumors. Jour. Cancer Res., 1920, v, 279-289.

102. Rohdenburg, G.L.; Bernhard, A. and Krehbiel, O.: Sugar tolerance in cancer. Jour. Am. Med. Assn., 1919, lxxii, 1528-1530.

103. Sajous, C.E. de M.: Disorders of the ductless glands. In: Da Costa, J.C.,Jr.: A handbook of medical treatment. Philadelphia, F.A.Davis Co., 1919, ii, 76-83.

104. Sajous, C.E. de M.: Adrenal insufficiency from the viewpoint of the clinician. Endocrinology, 1922, vi, 197-212.

105. Schulze, E. and Winterstein, E.: Über das Verhalten des Cholesterins gegen das Licht. Ztschr. f. physiol. Chem., 1904, xliii, 316-319.

106. Scott, W.J.M.: Influence of glands with internal secretion on the respiratory exchange. IV. Effect of suprarenal insufficiency in cats. Jour. Exper. Med., 1922, xxxvi, 199-217.

107. Sergent, E.: L'insuffisance surrénale devant les récentes critiques des physiologistes. Presse méd., 1921, xxix, 813-816. Abstr.: Endocrinology, 1922, vi, 284.

108. Sezary, A.: Des mélanodermies du type Addisonien. Presse méd., 1921, xxix, 281-283. Abstr.: Endocrinology, 1922, vi, 422.

109. Sittenfield, M.J.: The significance of the lymphocyte and immunity to cancer. Jour. Cancer Res., 1917, ii, 151-157.

110. Sivertson, I. and Dahlstrom, A.W.: The relation of muscular activity to carcinoma. Jour. Cancer Res., 1921, vi, 365-377.

111. Slemons: Quoted by Bailey.

112. Slye, Maud: The relation of inbreeding to tumor production: Studies in the incidence and inheritability of spontaneous tumors in mice. XIII. Problems in the behavior of tumors. Jour. Cancer Res., 1920, v, 53-79.

113. Sternberg, H.: Die Nebenniere bei physiologischer (Schwangerschaft-) und artifizieller Hypercholesterinämie. Beitr. z. path. Anat. u. z. allg. Path., 1915, lx, 91-123.

114. Stevens, R.H.: The blood in cancer under roentgenotherapy. Am. Jour. Roentgenol., 1917, iv, 215-246. Abstr.: Jour. Am. Med. Assn., 1916, lxvii, 1549.

115. Stewart, G.N.: Adrenal insufficiency. Endocrinology, 1921, v, 283-303.

116. Stewart, G.N.: The significance of the suprarenal glands in relation to the vital processes. In: Barker, L.F.: Endocrinology and Metabolism, New York, Appleton, 1922, ii, 127-168.

117. Stewart, G.N. and Rogoff, J.M.: Collected papers from the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University, Cleveland, 1918-1920, vi.

118. Suckling: Quoted by Sajous, 1919.

119. Timme, W.: Migraine. In: Nelson's Loose-leaf Living Medicine, 1920, vi, 654a-654h.

120. Vaughan, J.W.: Blood changes in malignancy and their prognostic significance. Tr. Assn. Res. and Ex-Res. Phys., Mayo Clinic, 1921, ii, 63-78.

121. Vincent, S.: Physiology, physiological chemistry, and experimental pathology of the female gonads (exclusive of the mammae and placenta). In: Barker, L.F.: Endocrinology and Metabolism. New York, Appleton, 1922, ii, 551-571.

122. Wagner and Rosenthal: Quoted by Grawitz.

123. Warthin, A.S.: Heredity with reference to carcinoma as shown by the study of the cases examined in the pathological laboratory of the University of Michigan, 1895-1913. Arch. Int. Med., 1913, xii, 546-555.

124. Warthin, A.S.: Family susceptibility to cancer. Jour. Michigan State Med. Soc., 1914, xiii, 34-39.

125. Warthin, A.S.: The pancreas as an endocrin gland. In: Barker, L.F.: Endocrinology and Metabolism. New York, Appleton, 1922, ii, 697-732.

126. Wells: Quoted by Crawford.

127. Windaus, A.: In Abderhalden, E.: Biochemisches Handlexikon. Berlin, Springer, 1911, iii, 270.

128. Wright, S.: Some observations on the nature and diagnostic significance of the white line of Sergent ("Ligne blanche surrenale"). Endocrinology, 1922, vi, 493-510.

129. Zülser: Quoted by Warthin.

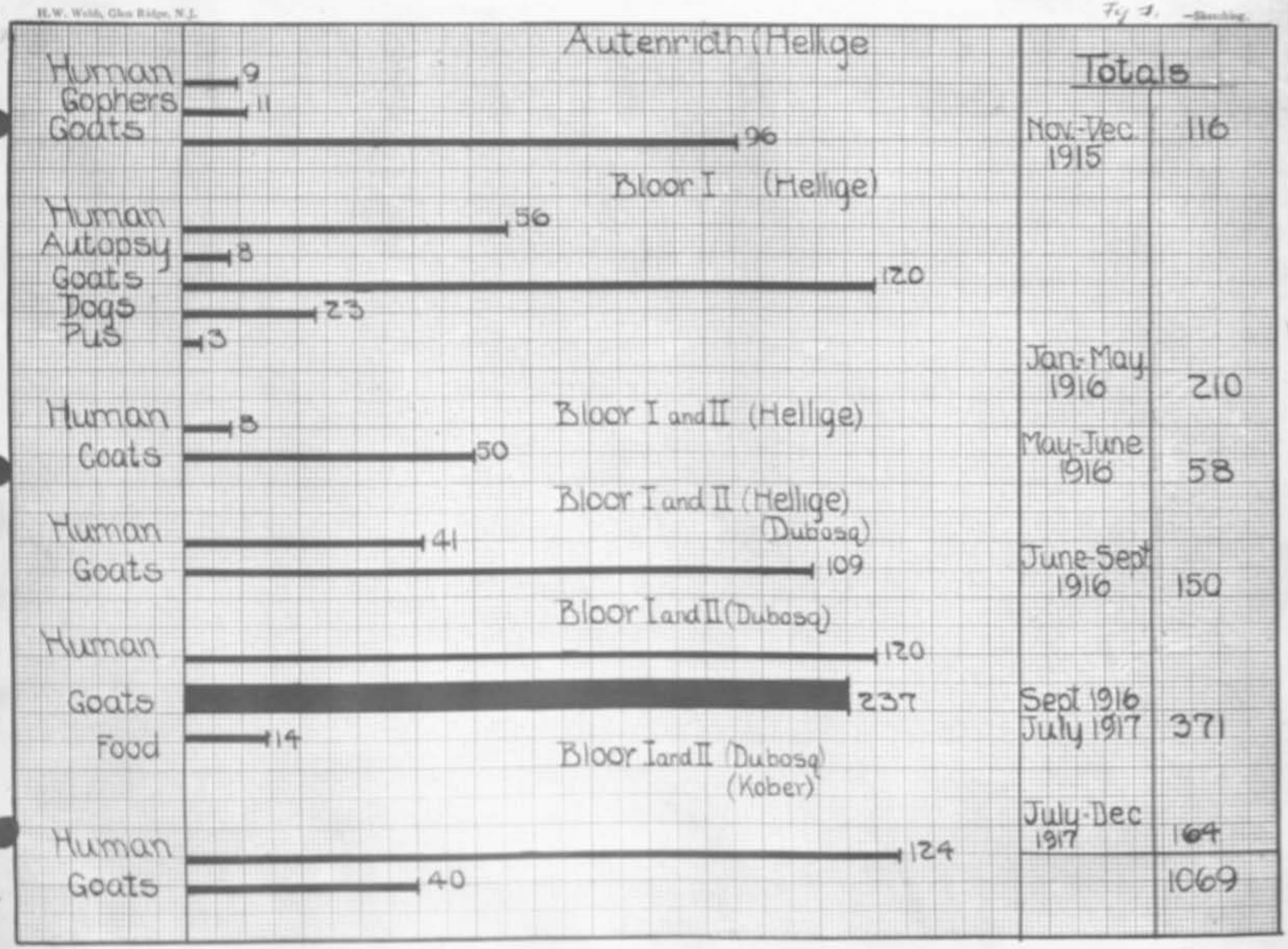

H.W. Walsh, Glen Ridge, N.J.
Autenrieth (Hellige
Human
Gophers
Goats
9
11
96
Bloor I (Hellige)
Human
Autopsy
Goats
Dogs
Pus
56
8
120
23
3
Bloor I and II (Hellige)
Human
Goats
8
50
Bloor I and II (Hellige) (Dubosq)
Human
Goats
41
109
Bloor I and II (Dubosq)
Human
Goats
Food
120
237
14
Bloor I and II (Dubosq) (Kober)
Human
Goats
124
40
Totals
Nov.-Dec. 1915
116
Jan.-May 1916
210
May-June 1916
58
June-Sept 1916
150
Sept 1916 July 1917
371
July-Dec 1917
164
1069

Fig. 1.

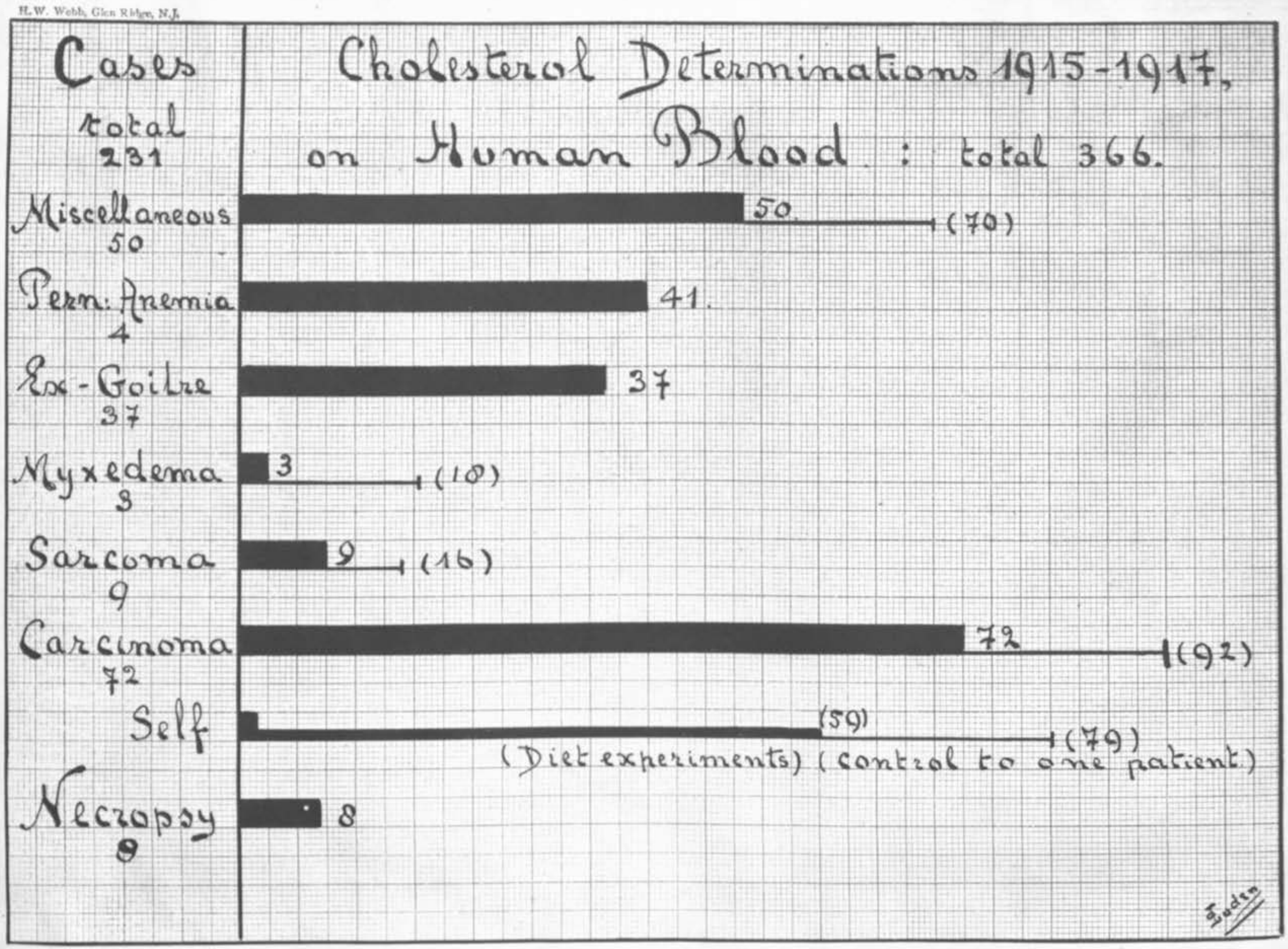

H.W. Webb, Glen Ridge, N.J.
Cases
total
231
Cholesterol Determinations 1915-1917,
on Human Blood : total 366.
Miscellaneous
50
50.
(70)
Pern: Anemia
4
41.
Ex-Goitre
37
37
Myxedema
3
3
(18)
Sarcoma
9
9
(16)
Carcinoma
72
72
(92)
Self
(59)
(79)
(Diet experiments) (control to one patient)
Necropsy
8
8

Fig. 2.

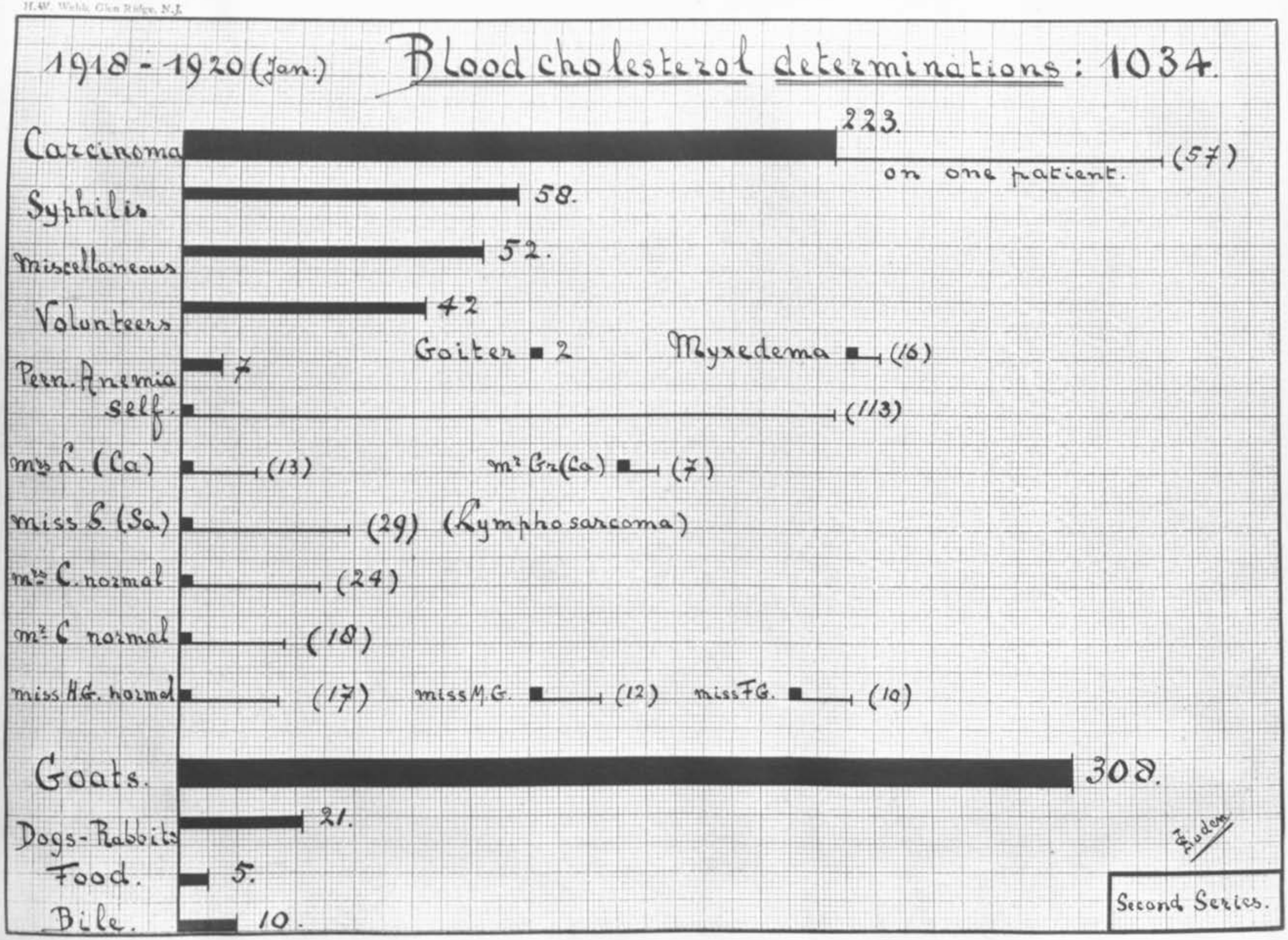

H.W. Webb, Glen Ridge, N.J.
1918 - 1920 (Jan.)
Blood cholesterol determinations: 1034.
Carcinoma
223.
(57)
on one patient.
Syphilis
58.
Miscellaneous
52.
Volunteers
42
Goiter 2
Myxedema (16)
Pern. Anemia
7
self.
(113)
mrs L. (Ca)
(13)
mr Gr(Ca)
(7)
miss S. (Sa.)
(29)
(Lymphosarcoma)
mrs C. normal
(24)
mr C normal
(18)
miss H.G. normal
(17)
miss M.G.
(12)
miss F.G.
(10)
Goats.
308.
Dogs-Rabbits
21.
Food.
5.
Bile.
10.
Second Series.

Fig. 3.

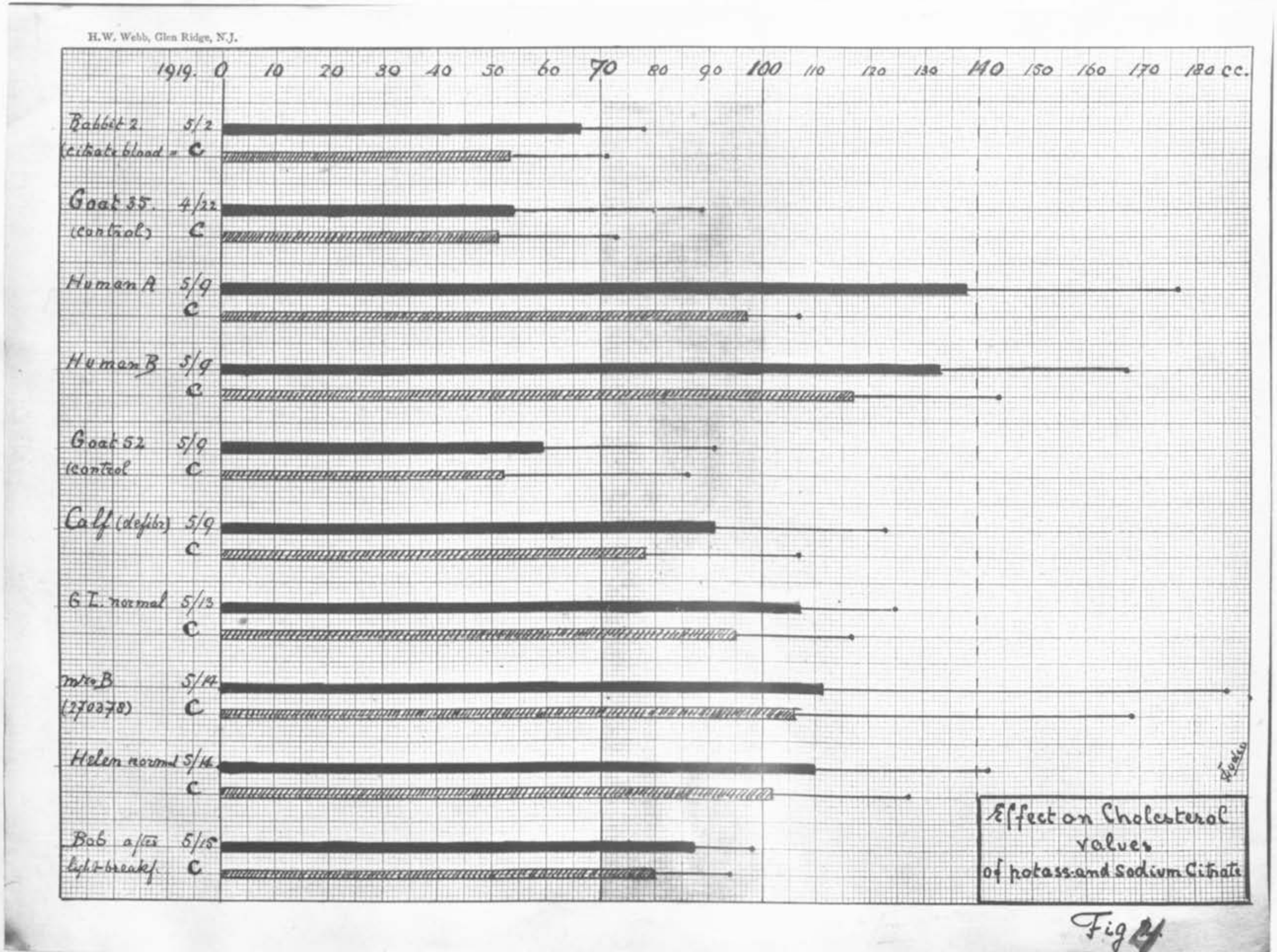
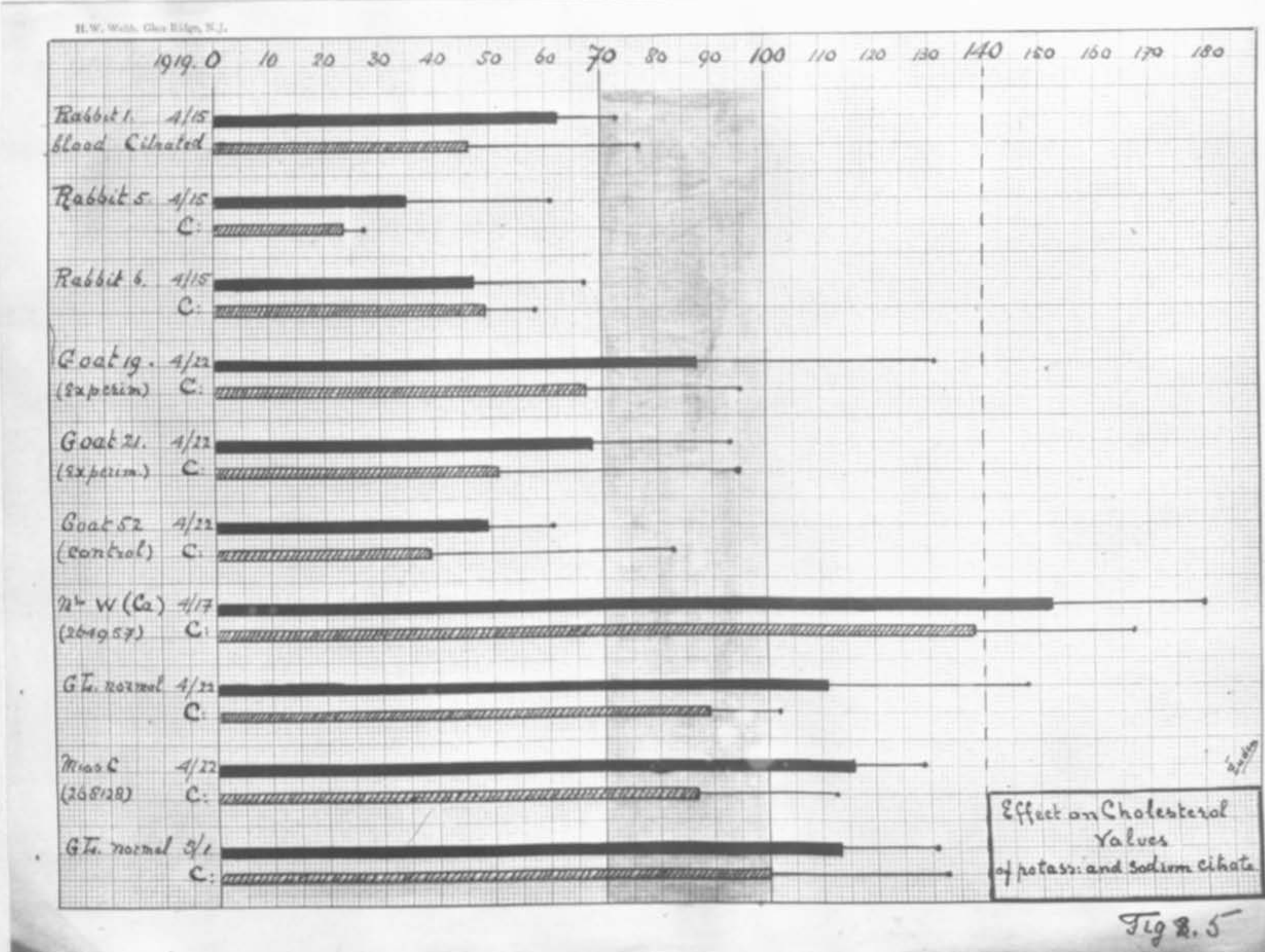

H.W. Webb, Glen Ridge, N.J.
1919. 0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 cc.
Rabbit 2 5/2
(citrate blood = C
Goat 35. 4/22
(control) C
Human A 5/9
C
Human B 5/9
C
Goat 52 5/9
(control C
Calf (defib.) 5/9
C
G.L. normal 5/13
C
mrs B 5/14
(270078) C
Helen normal 5/16
C
Bob after 5/15
light breakf. C
Effect on Cholesterol values of potass. and Sodium Citrate
Fig 4

Fig. 4.



H. W. Webb, Glen Ridge, N.J.
1919. 0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180
Rabbit 1. 4/15
blood Citrated
Rabbit 5. 4/15
C:
Rabbit 6. 4/15
C:
Goat 19. 4/22
(Experim) C:
Goat 21. 4/22
(Experim.) C:
Goat 52 4/22
(control) C:
Mr W (Ca) 4/17
(264957) C:
G.T. normal 4/22
C:
Miss C 4/22
(268128) C:
G.T. normal 5/1
C:
Effect on Cholesterol Values of potass: and sodium citrate
Fig 2. 5

Fig. 5.

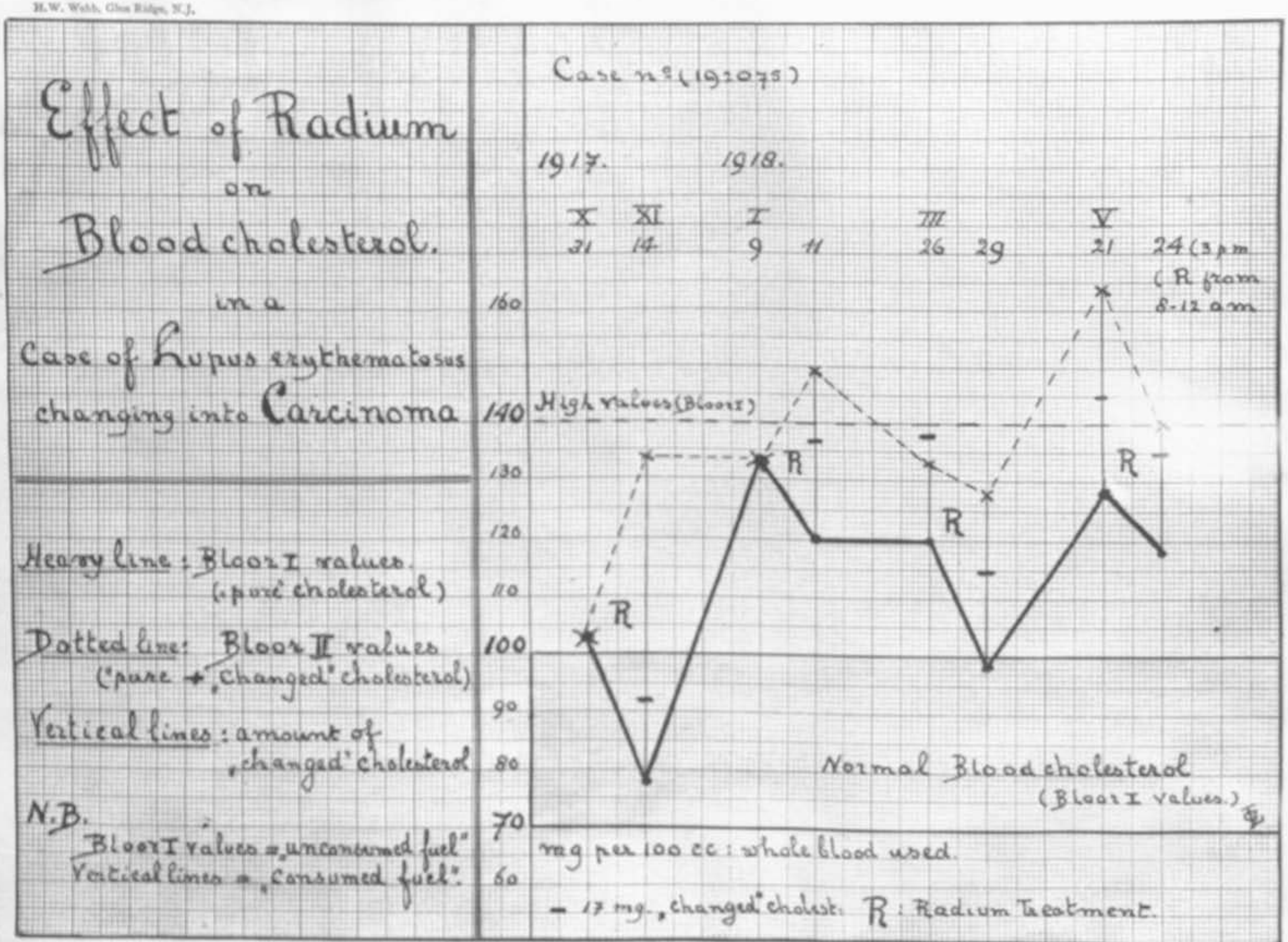

H.W. Webb, Glen Ridge, N.J.
Effect of Radium
on
Blood cholesterol.
in a
Case of Lupus erythematosus
changing into Carcinoma
Heavy line: Bloor I values.
(„pure" cholesterol)
Dotted line: Bloor II values
(„pure + „changed" cholesterol)
Vertical lines: amount of
„changed" cholesterol
N.B.
Bloor I values = „unconsumed fuel"
Vertical lines = „consumed fuel".
Case no (192075)
1917.
1918.
X
XI
I
III
V
21
14
9
11
26
29
21
24 (3 pm
(R from
8-12 am
160
140
130
120
110
100
90
80
70
60
High values (Bloor I)
R
Normal Blood cholesterol
(Bloor I values.)
mg per 100 cc: whole blood used.
– 17 mg. „changed" cholest. R: Radium Treatment.

Fig. ~~4~~. 6

Fig. 6.

Legends

Fig. 1. Cholesterol determinations made by the writer from November, 1915 to December, 1917. Methods used: Autenrieth-Funk, and Bloor I and II. Colorimeters: Hellige, Hellige-Dusbosq, Dusbosq-Kober; hyphenated designation of two colorimeters indicates parallel determinations with both instruments. Samples used in the determinations are given in margin: human blood, goat's blood, human pus, and so forth. Fourth entry from the bottom has been drawn in double width on account of the number of determinations; goat's blood, 237.

Fig. 2. Human blood, cholesterol determinations under various conditions. Wide bar denotes total number of determinations made on individual cases. Narrow bar and number in brackets denotes additional determinations on the same person. Necropsy: blood taken at necropsy at various hours after death, to study effect of postmortem changes; cholesterol values were not changed.

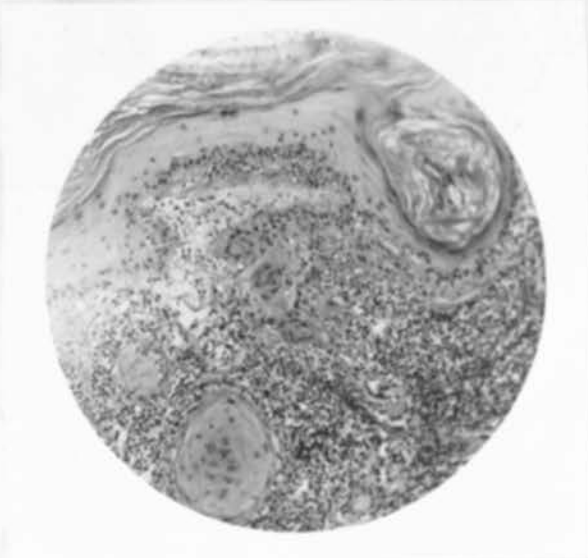
Fig. 3. Cholesterol determinations made by the writer from 1918 to 1920. Wide bar denotes total number of determinations; narrow bar and number in brackets denotes additional determinations on the same person.

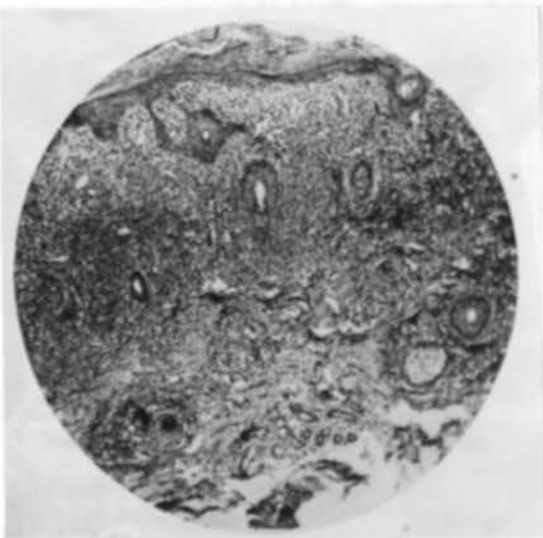
Figs. 4 and 5. Diagrams showing effect of addition of sodium and potassium citrate to blood sample on blood cholesterol values. Note irregularity of the changes in the Bloor I (wide bar) and of the Bloor II (narrow bar) cholesterol values by comparing the upper, solid black bar (pure blood sample) with the lower, striped bar (sample to which the citrates C was added).

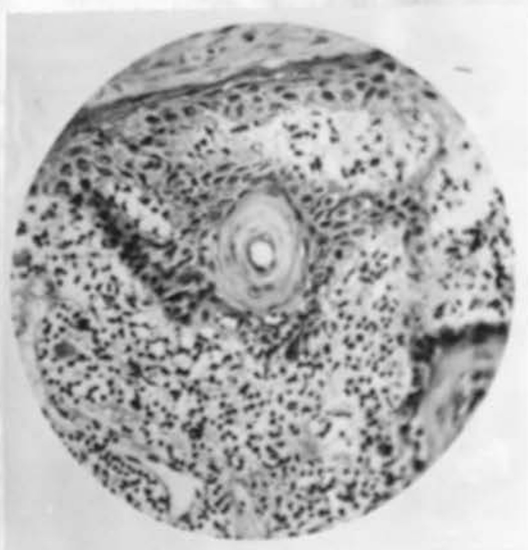
Fig. 6. Diagram showing effect of radium treatment on blood cholesterol values in lupus erythematosus of the nose degenerating into carcinoma (Case A192075). The amount of split cholesterol is indicated by the vertical line, representing the difference between the Bloor I and II cholesterol values; the length of the line is proportionate to the number of milligrams of split cholesterol for each 100 c.c. of whole blood. The normal minimum (17 mg.) is indicated by the small horizontal bar on the vertical line; the bar is above the line when the

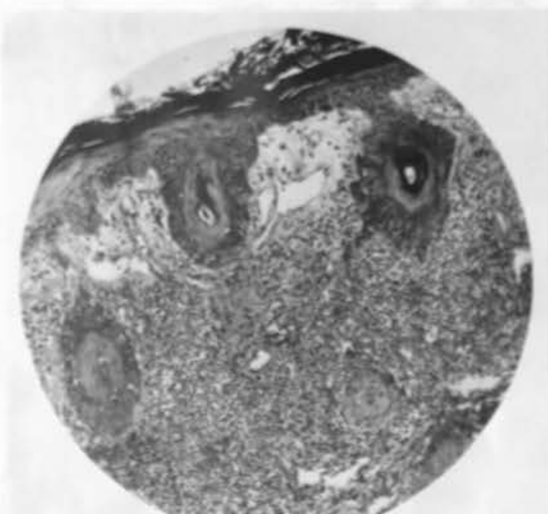
amount falls below the normal minimum. The star or crossed dot indicates the total absence of split cholesterol, when the Bloor I and II values are identical.

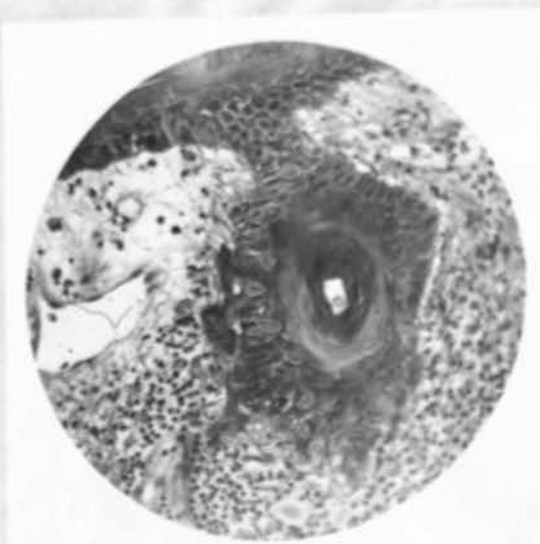
Figs. 7 and 8. (Case A192075). Lupus erythematosus of the nose degenerating into carcinoma: picture taken four weeks after the first radium treatment, the lesions are much less severe than they were initially.











Figs. 9, 10, 11, 12 and 13.

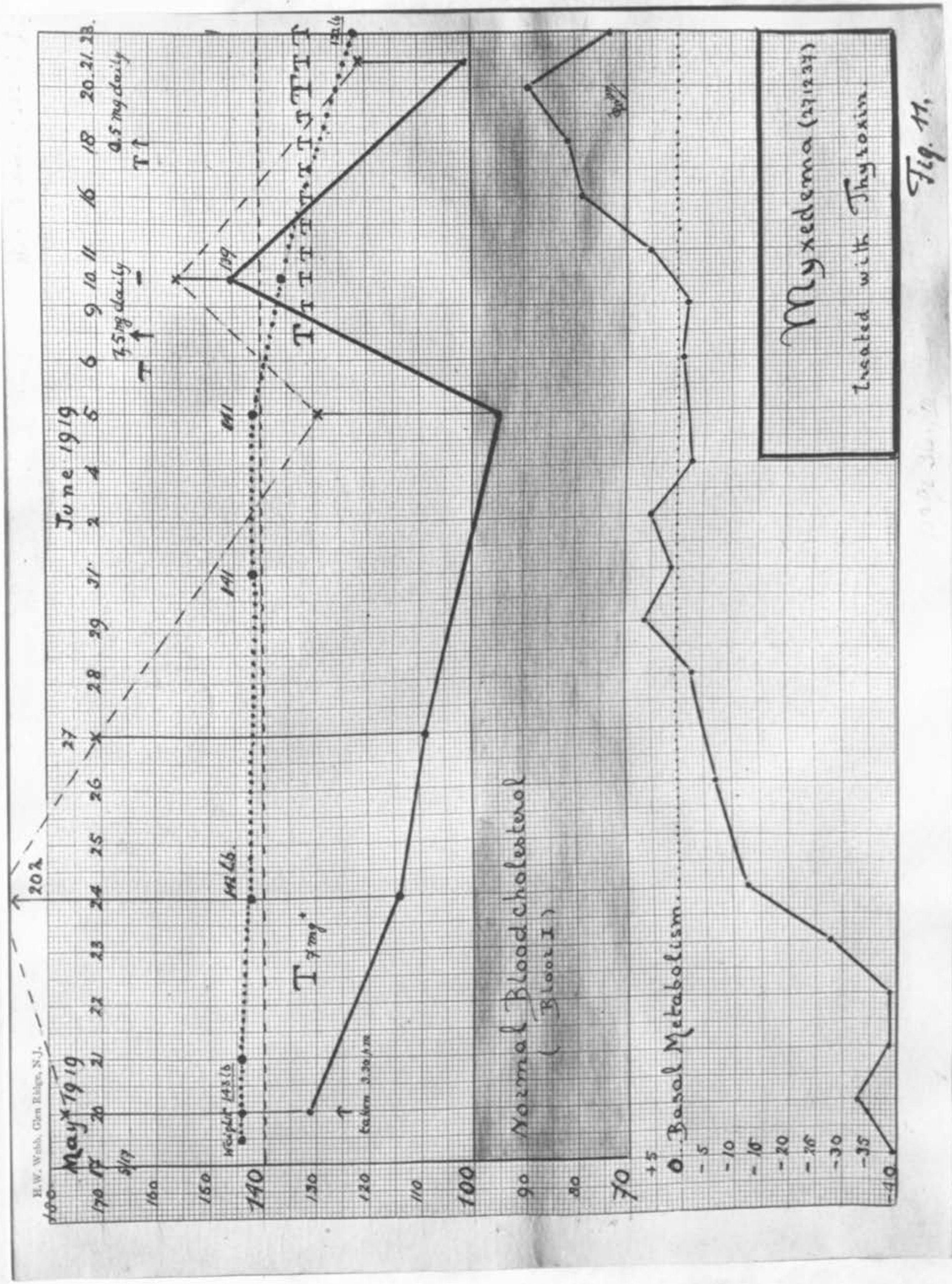

Myxedema (271237)
treated with Thyroxin.
Fig. 11.
June 1919
May 1919
Normal Blood cholesterol
(Bloor I)
Basal Metabolism
E.W. Webb, Glen Ridge, N.J.

FIG. 14.

Fig. 15.

Fig. 16.

Fig. 17.

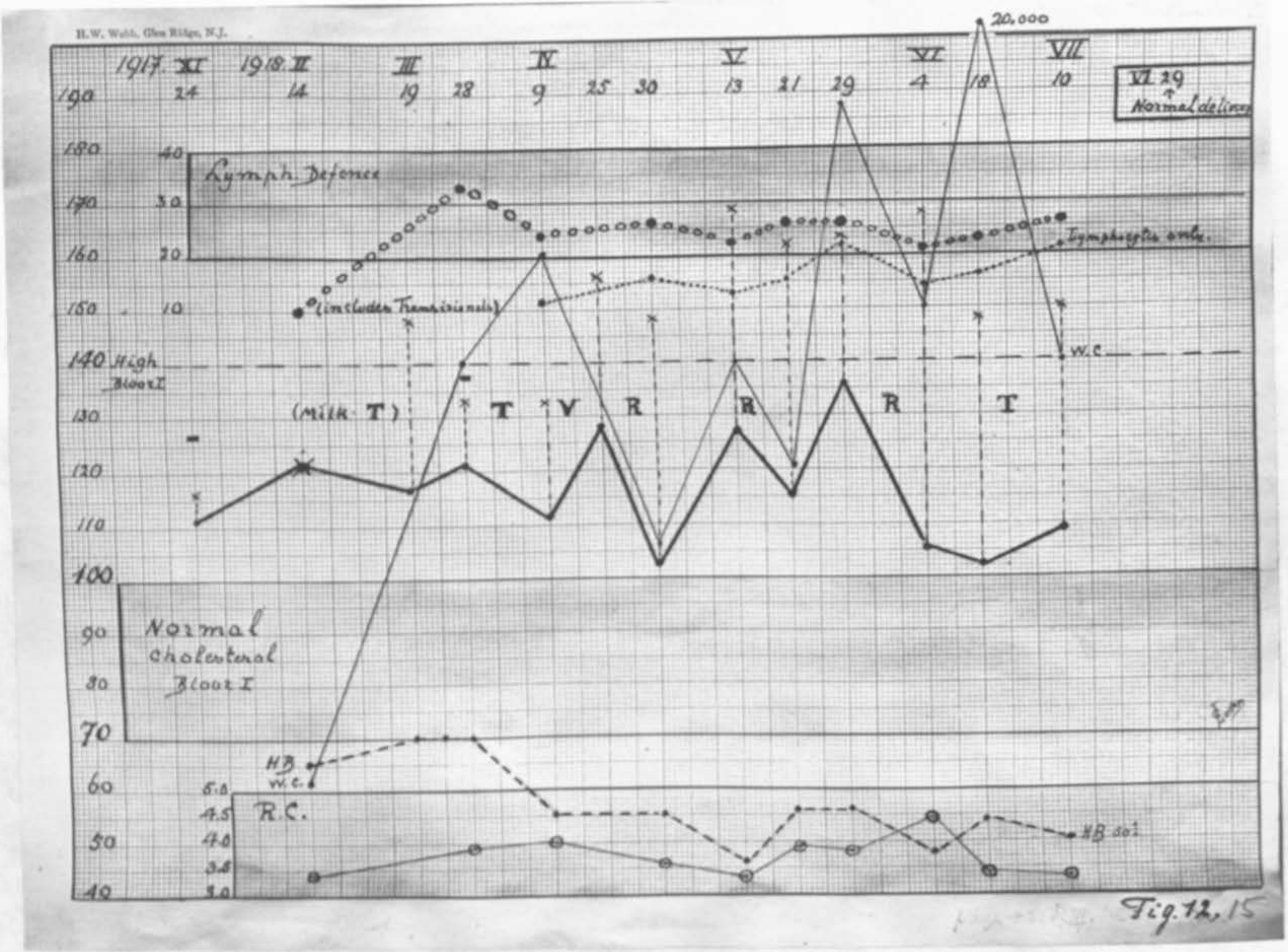

H. W. Webb, Glen Ridge, N.J.
1917. XI 24
1918. II 14
III 19 28
IV 9 25 30
V 13 21 29
VI 4 18
VII 10
20,000
VI. 29 Normal delivery
Lymph. Defence
(includes Transitionals)
Lymphocytes only.
140 High Blood I
(Milk T)
T
V
R
R
R
T
W.C.
Normal cholesterol Blood I
H.B.
W.C.
R.C.
H.B. 80%
Fig. 12, 15

Fig. 18.

Legends

Figs. 9, 10, 11, 12, and 13. (Case A192075). Serial sections of lupus erythematosus of the nose showing degeneration into carcinoma.

Fig. 14. (Case A271237). Diagram of the effect of thyroxin on the blood cholesterol values in myxedema. Note the inverse relation between blood cholesterol and metabolic rate. The large amount of split cholesterol (vertical line) May 20, when the metabolic rate was -35, may be explained by the fact that the blood could be obtained only at 3:30 p.m., at the height of digestion of the midday meal, whereas the metabolic rate had been established before breakfast. All the other determinations of the blood cholesterol were made before breakfast.

Fig. 15. (Case A171479). Recurrent carcinoma of the breast complicated by pregnancy (fifth month), February 16, 1918.

Fig. 16. (Case A171479). Recurrent carcinoma of the breast complicated by pregnancy, after six weeks of exclusive milk diet, March 28, 1918.

Fig. 17. (Case A171479). Recurrent carcinoma of the breast complicated by pregnancy, after two weeks of mixed diet, including meat, May 14, 1918. Patient got tired of milk diet.

Fig. 18. (Case A171479). Diagram showing effect of milk diet, thyroxin (T), prophylactic vaccine against influenza (V) and radium (R) on the blood cholesterol values in recurrent carcinoma of the breast complicated by pregnancy. Note the initial absence of split cholesterol, small vertical bar and crossed dot November 24, 1917 and February 14, 1918; the increase of the split cholesterol in the later entries, which is particularly marked after radium treatment and accompanied by a drop of the Bloor I values (heavy line). The thin line (W.C.) represents the total leukocyte count, and the small dotted line the "lymphoid defence", which is persistently low. Pregnancy terminated in normal delivery June 29, 1918. The patient died of influenzal pneumonia October 15, 1918. Necropsy, no lung metastasis; the patient lived much longer and did far better on the

whole than her condition seemed to forecast at first.

Fig. 19. Child, aged twelve months, of patient with recurrent carcinoma of the breast complicated by pregnancy (Case A171479).

Fig. 20. Same child as Figure 19, aged eighteen months.

Fig. 21. Same child as Figure 19, aged four years. The little girl has a sunny disposition, is very active and has been very well, although she seemed very delicate as a baby.

H.W. Webb Glen Ridge, N.J.

Key to Diagrams of Blood Constituents.

Figures 23-42.

LD :	Lymphoid defence :	....	- in percentage
C :	Blood catalase :	×—×—×	- in percentage
BI :	Blood cholesterol :	━━•━━	Bloor I Values; mg p. 100 cc.
WC :	Total leucocytes :	•—•—•	- in thousands.
BS :	Blood sugar :	o—o—o	- mg per 100 cc.
HB :	Hemoglobin :	•----•----•	- in percentage
R.C :	Erythrocytes :	⊙—⊙—⊙	- in millions.
	Vertical broken lines	┆ ┆ ┆ ┆	- Cholesterol splitproducts, in mg.

The figures 40-200 apply to all determinations.

Examples: 100 = Cholesterol 100 mg p 100 cc ; W.C. 10 000 ; HB 100 %
45 = Blood sugar 0.045 % ; R.C 4.5 millions.

A special scale 20-40 is given for LD and C.

Fig. 22.

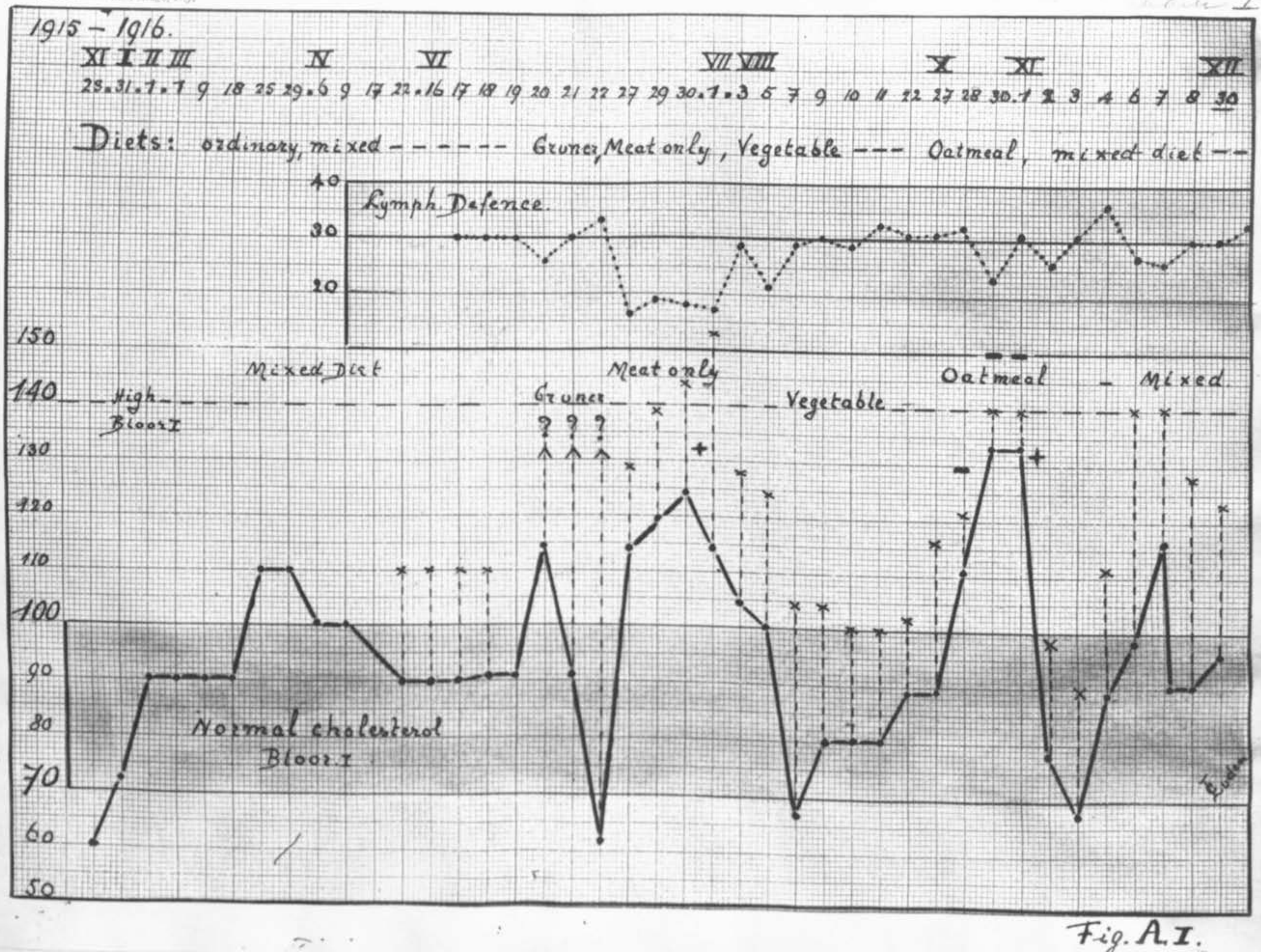

1915 – 1916.
XI XII I II III IV VI VII VIII X XI XII
Diets: ordinary, mixed ------ Gruner, Meat only, Vegetable --- Oatmeal, mixed diet --
Lymph. Defence.
Mixed Diet
High Blood I
Gruner
Meat only
Vegetable
Oatmeal - Mixed.
Normal cholesterol Blood I
Fig. A.I.

Fig. 23.

-19-

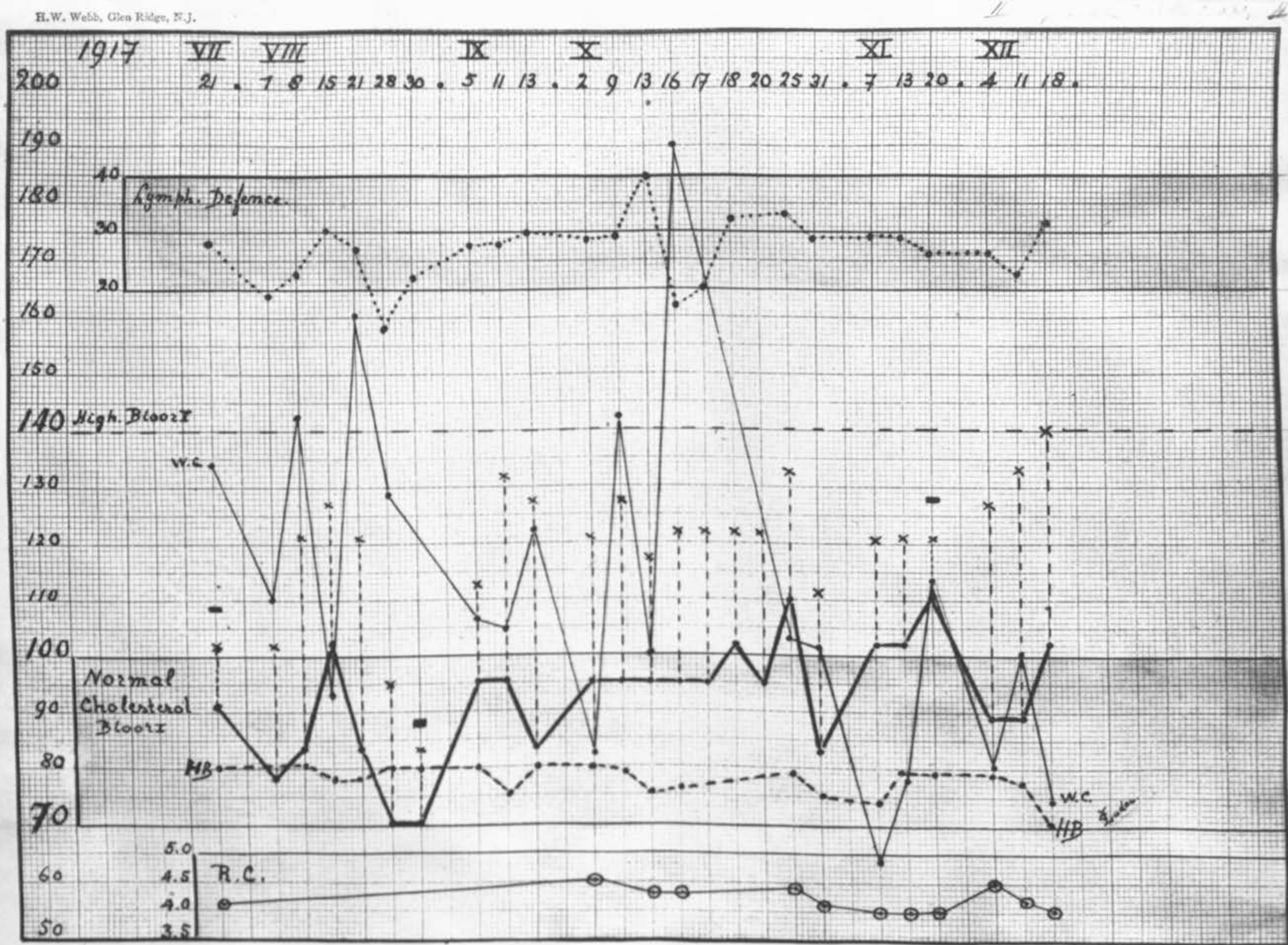


Fig. A.II

Fig. 24.

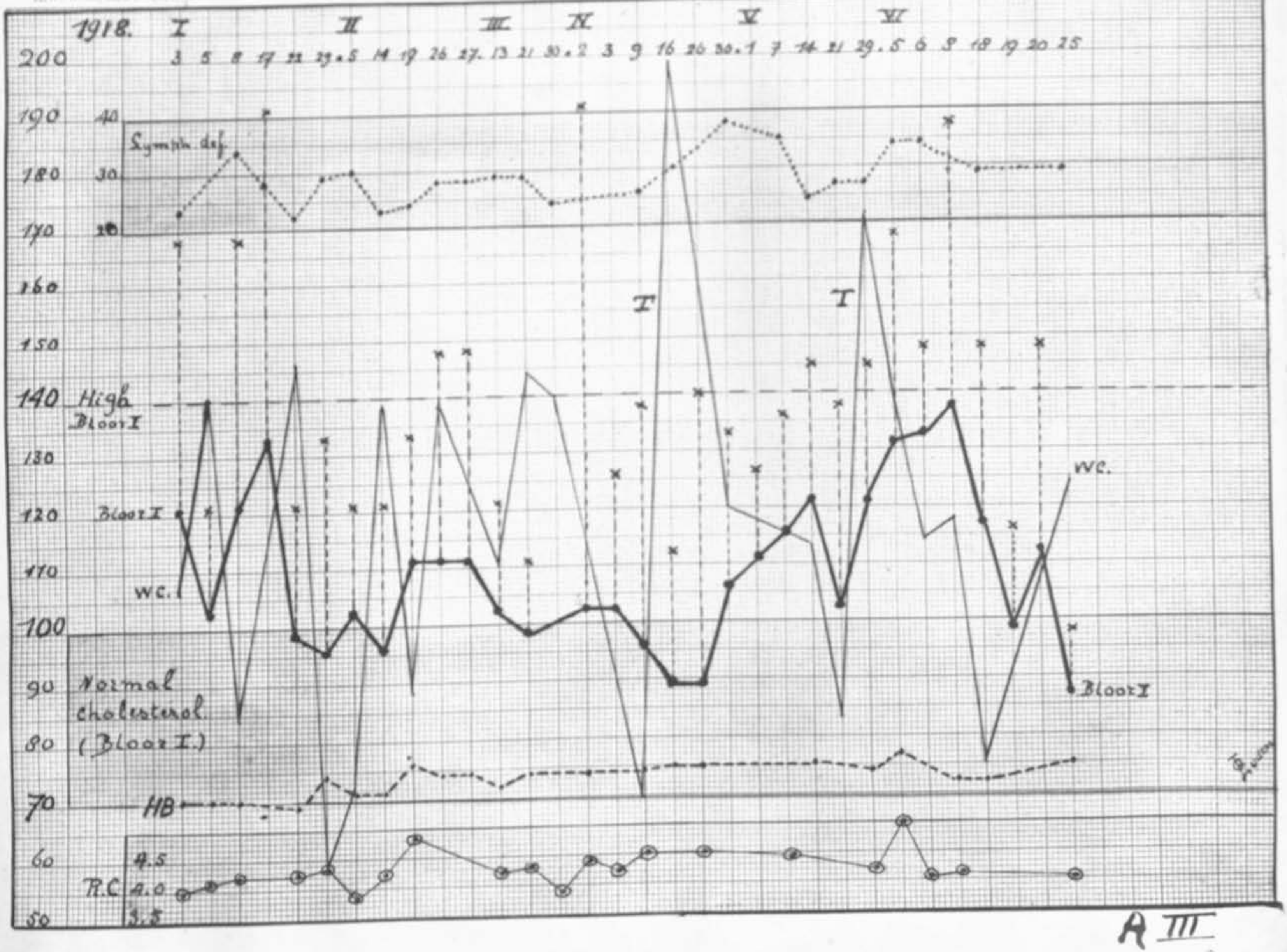

1918.
I
II
III
IV
V
VI
3 5 8 17 22 29. 5 14 19 26 27. 13 21 30. 2 3 9 16 20 30. 1 7 14 21 29. 5 6 8 18 19 20 25
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
Sympth. def.
High Bloor I
Bloor I
WC.
I
Normal cholesterol (Bloor I.)
HB
R.C
4.5
4.0
3.5
A III

Fig. 25.

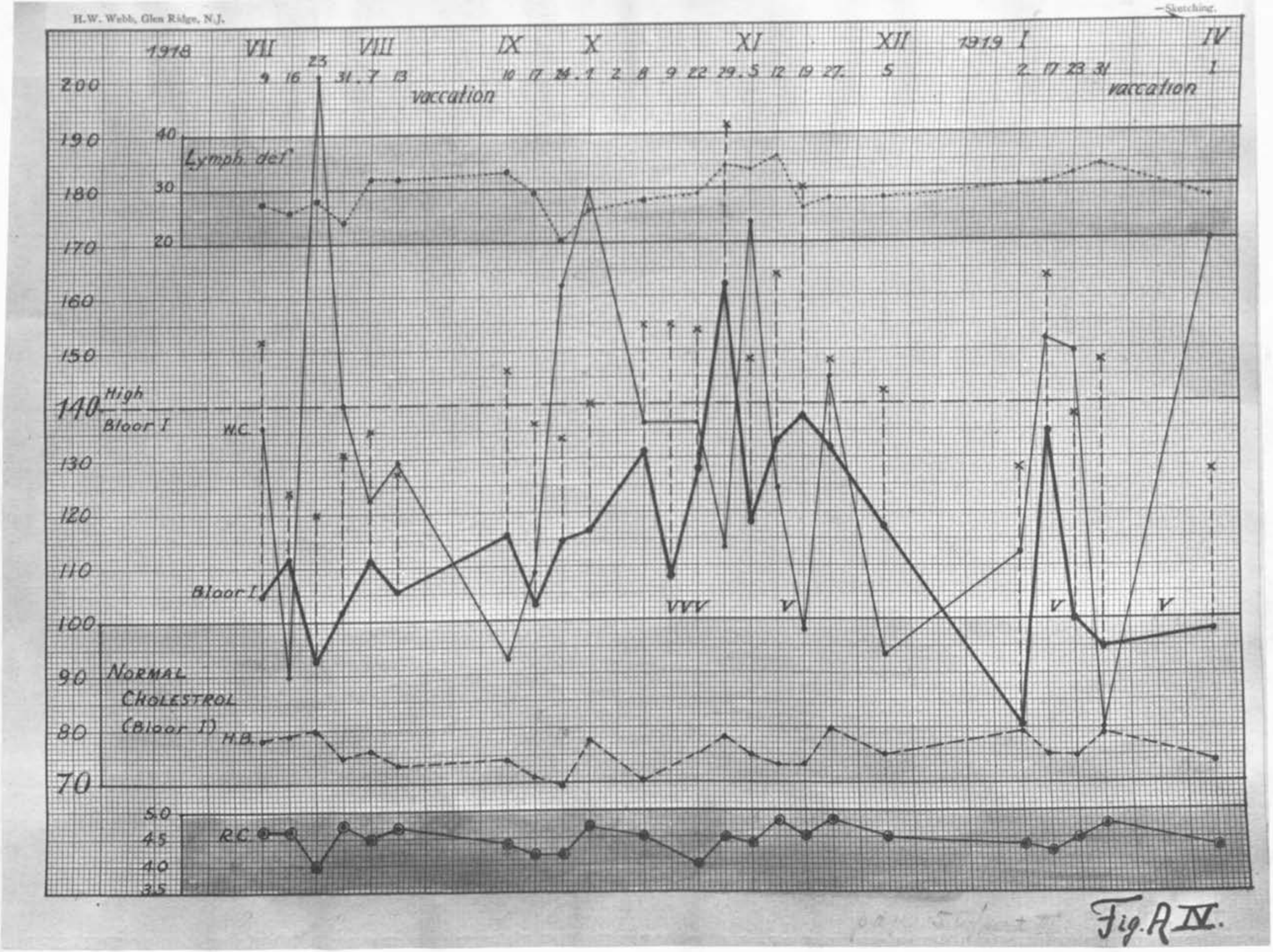

H.W. Webb, Glen Ridge, N.J.
Sketching.
1918 VII VIII IX X XI XII 1919 I IV
9 16 23 31. 7 13 10 17 24. 1 2 8 9 22 29. 5 12 19 27. 5 2. 17 23 31 1
vaccation
vaccation
Lymph. def.
40
30
20
200
190
180
170
160
150
140
130
120
110
100
90
80
70
High
Bloor I
W.C.
Bloor I.
VVV
V
V
V
Normal
Cholestrol
(Bloor I)
H.B.
R.C.
5.0
4.5
4.0
3.5
Fig. A IV.

Fig. 26.

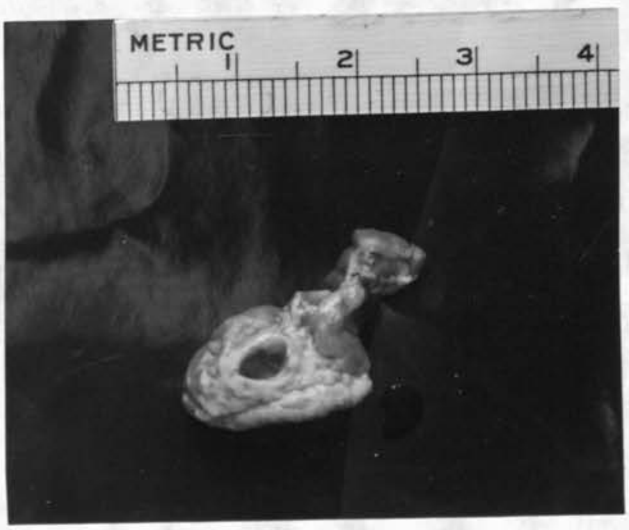


Fig. 26a.

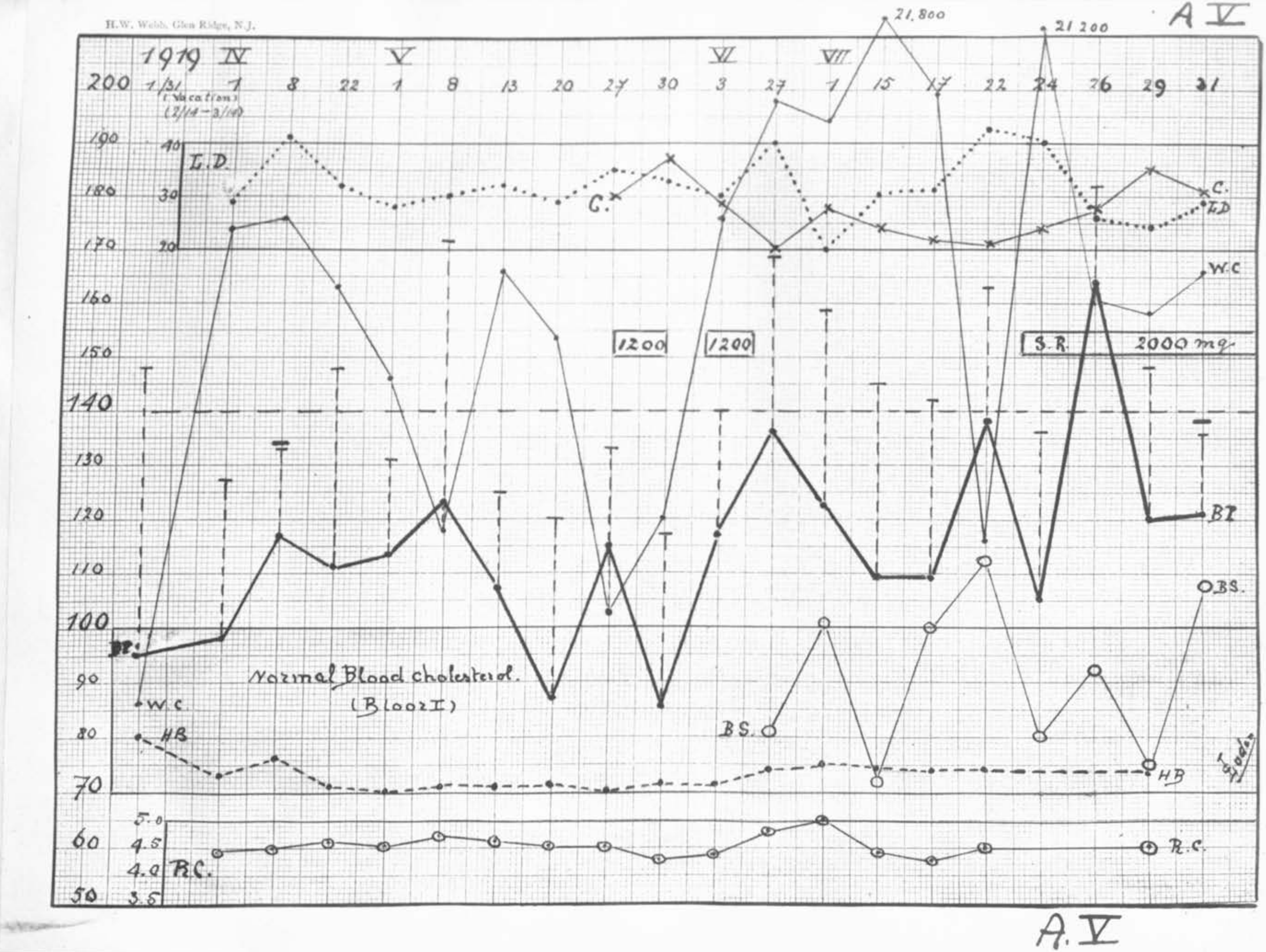

H.W. Webb, Glen Ridge, N.J.
A V
1919 IV
V
VI
VII
1/31
(Vacation) (2/14–3/10)
21,800
21,200
L.D.
C.
W.C
BP
BS.
HB
R.C.
1200
1200
S.R.
2000 mg.
Normal Blood cholesterol. (Bloor I)
A. V

Fig. 27.

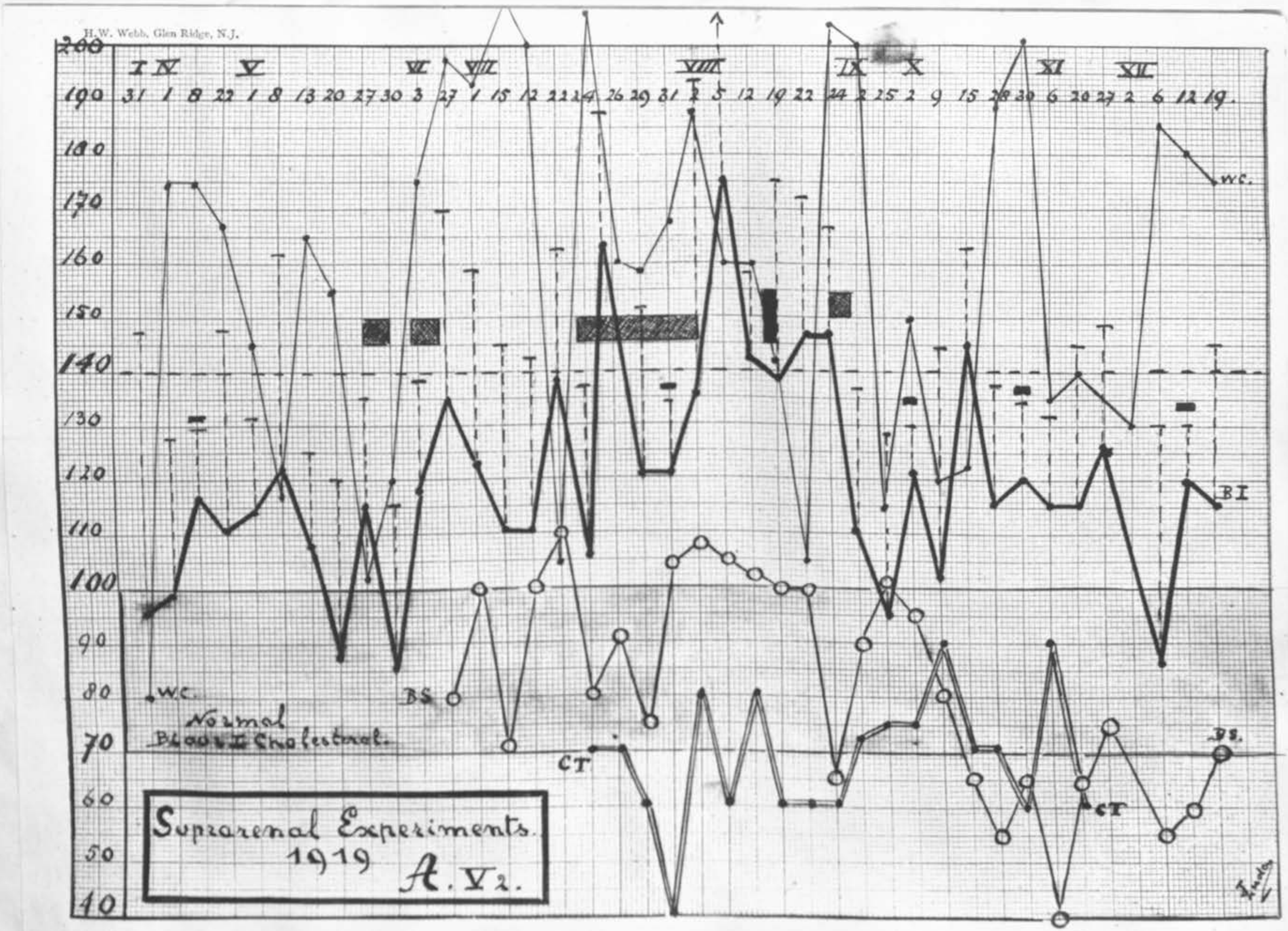

H.W. Webb, Glen Ridge, N.J.
W.C.
Normal
Blood Cholesterol.
BS
CT
BI
BS.
Suprarenal Experiments.
1919
A. V2.

Fig. 28.

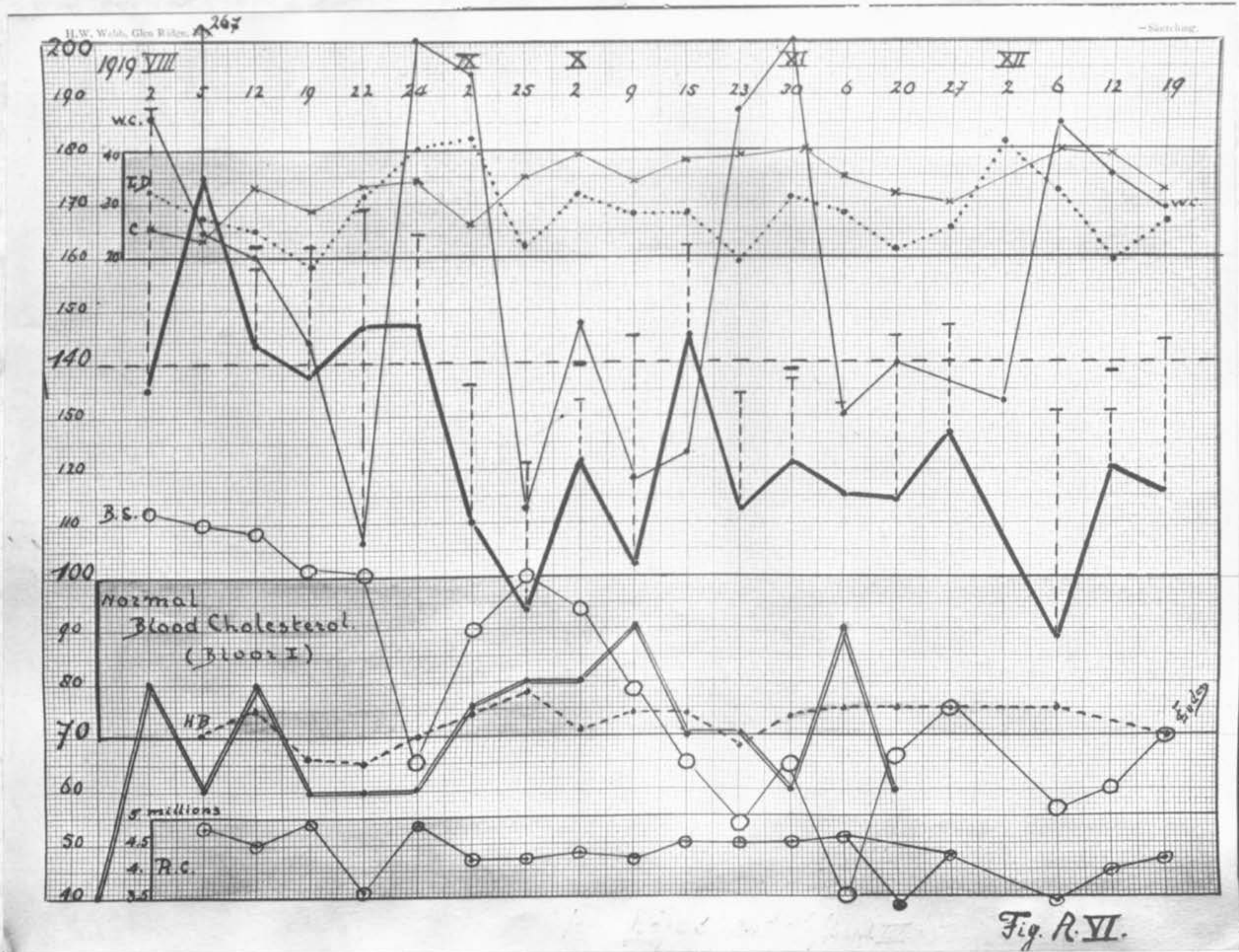

1919 VIII
IX
X
XI
XII
2
5
12
19
22
24
2
25
2
9
15
23
30
6
20
27
2
6
12
19
267
W.C.
T.D.
C
B.S.
H.B.
R.C.
5 millions
Normal
Blood Cholesterol
(Bloor I)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
Fig. R. VI.

Fig. 29.

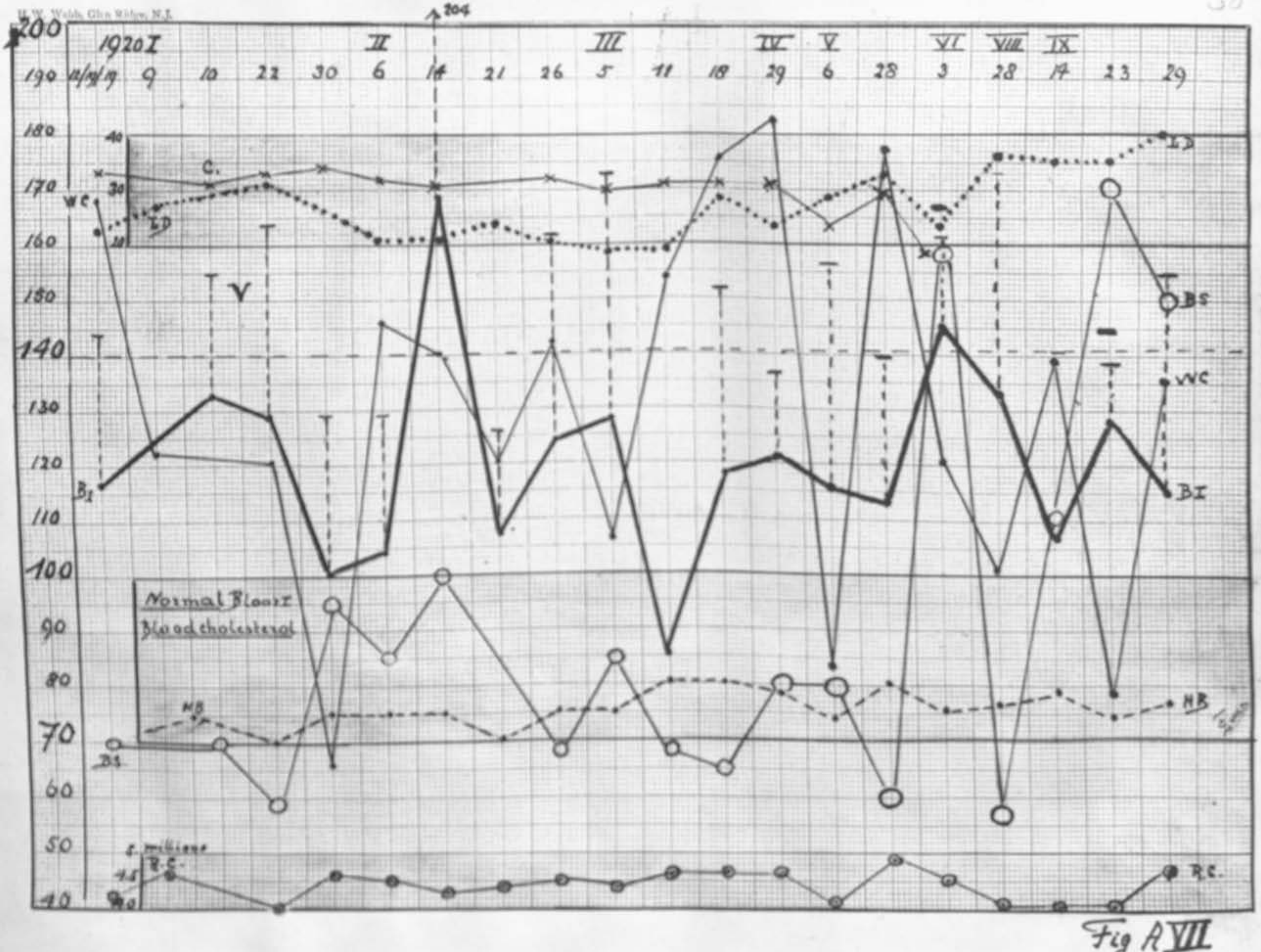
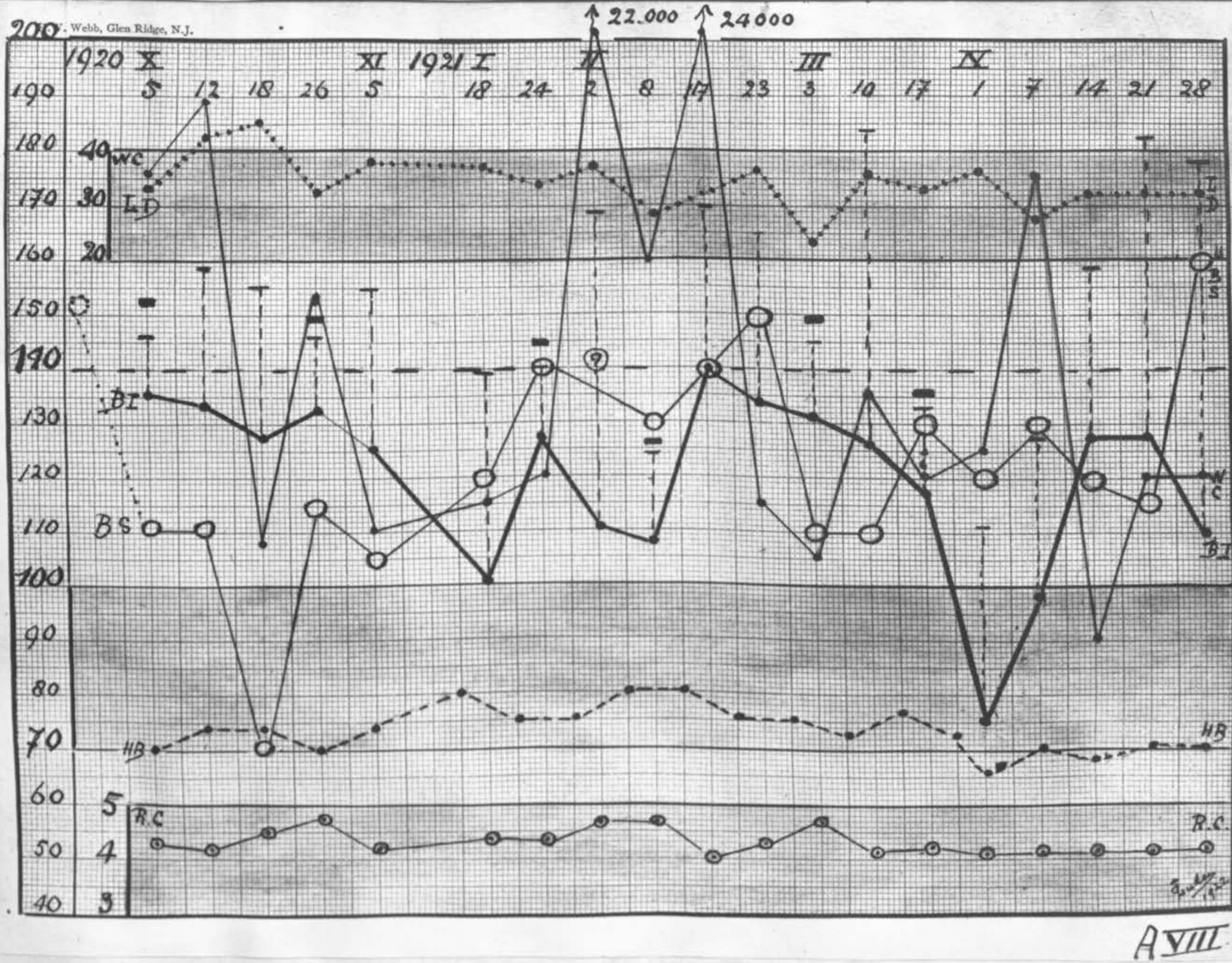

1920 I
II
III
IV
V
VI
VIII
IX
12/19/19
9
10
22
30
6
14
21
26
5
11
18
29
6
28
3
28
14
23
29
204
Normal Blood
Blood cholesterol
WC
C.
LD
BS
VVC
BI
HB
RC.
Fig A VII

Fig. 30.



Webb, Glen Ridge, N.J.
1920 X
XI 1921 I
II
III
IV
5 12 18 26 5 18 24 2 8 17 23 3 10 17 1 7 14 21 28
22.000
24000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
40
30
20
5
4
3
WC
LD
BI
BS
HB
R.C
A VIII

Fig. 31.

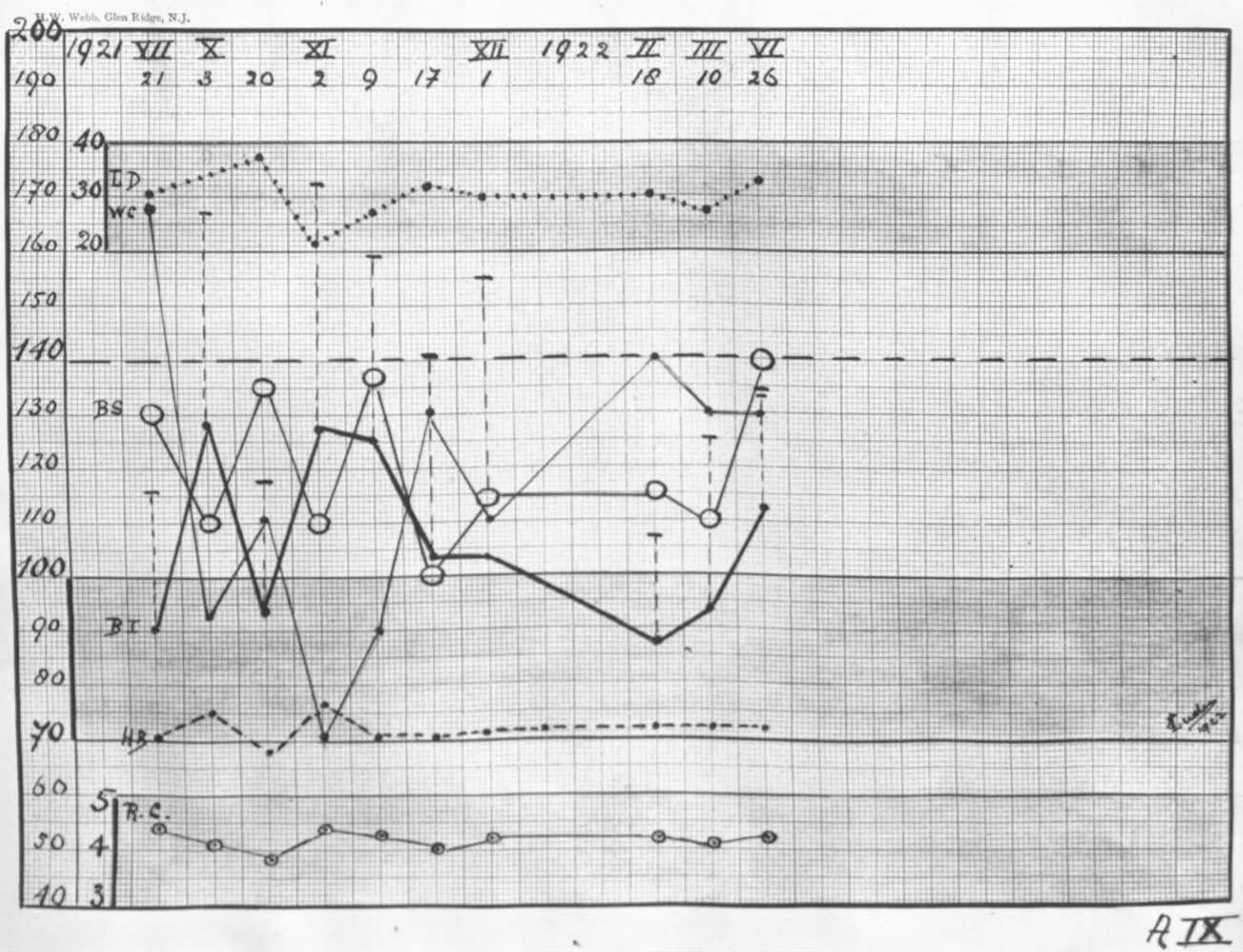

H.W. Webb, Glen Ridge, N.J.
1921 VII 21
X 3
20
XI 2
9
17
XII 1
1922 II 18
III 10
VI 26
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
40
30
20
LD
WC
BS
BI
HB
5
4
3
R.C.
R IX

Fig. 32.

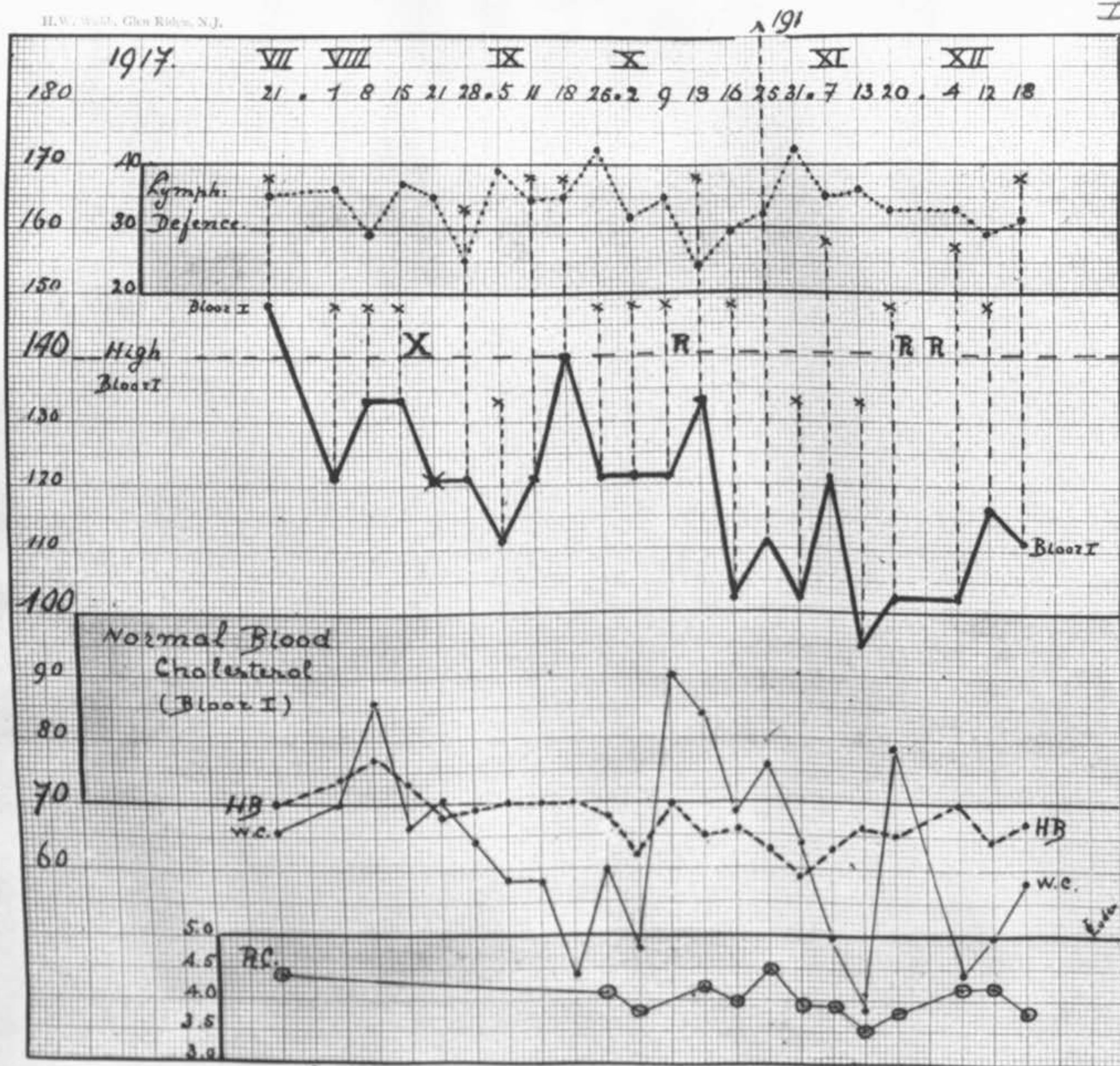


Fig. BI.

Fig B I

Fig. 33.

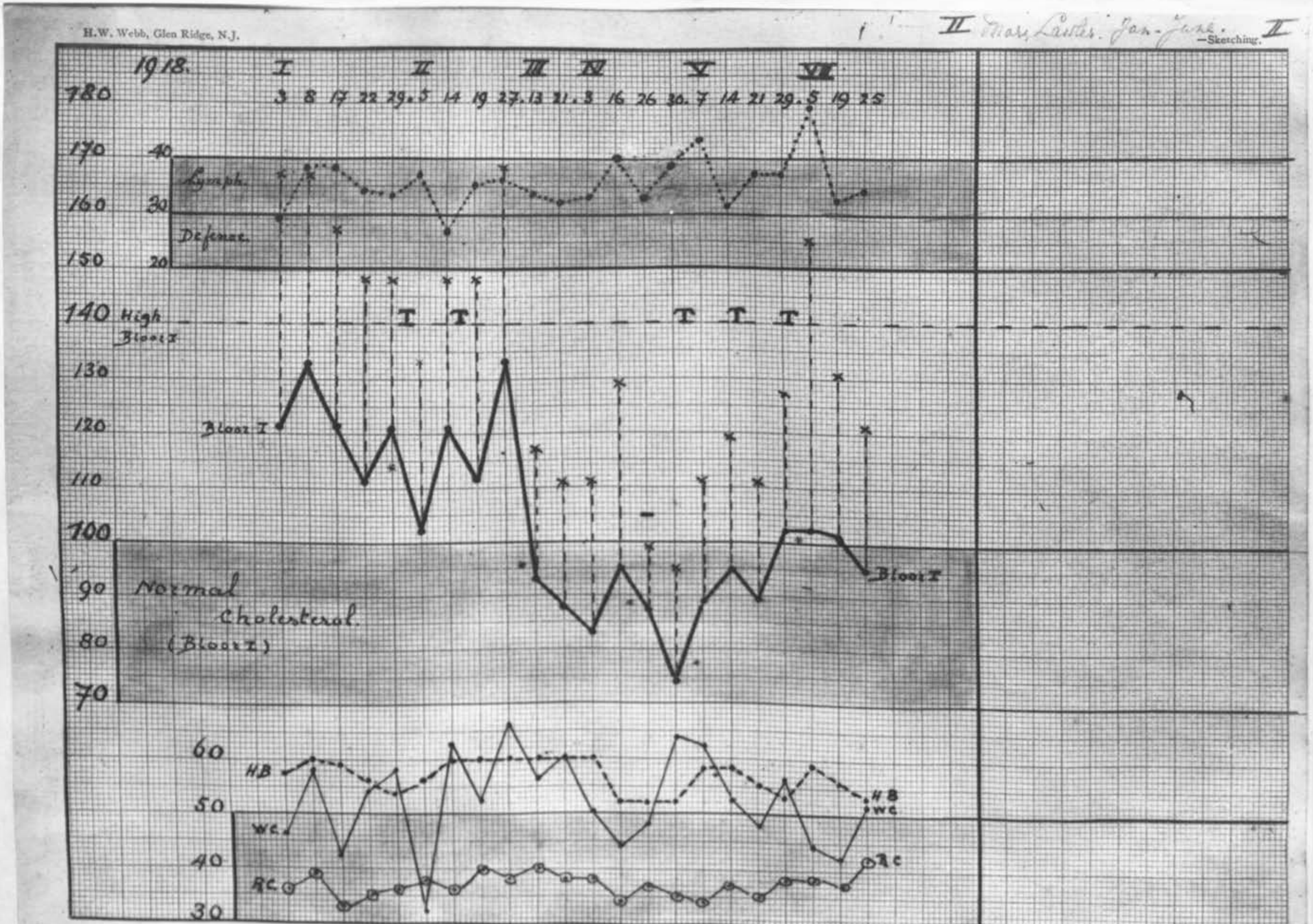
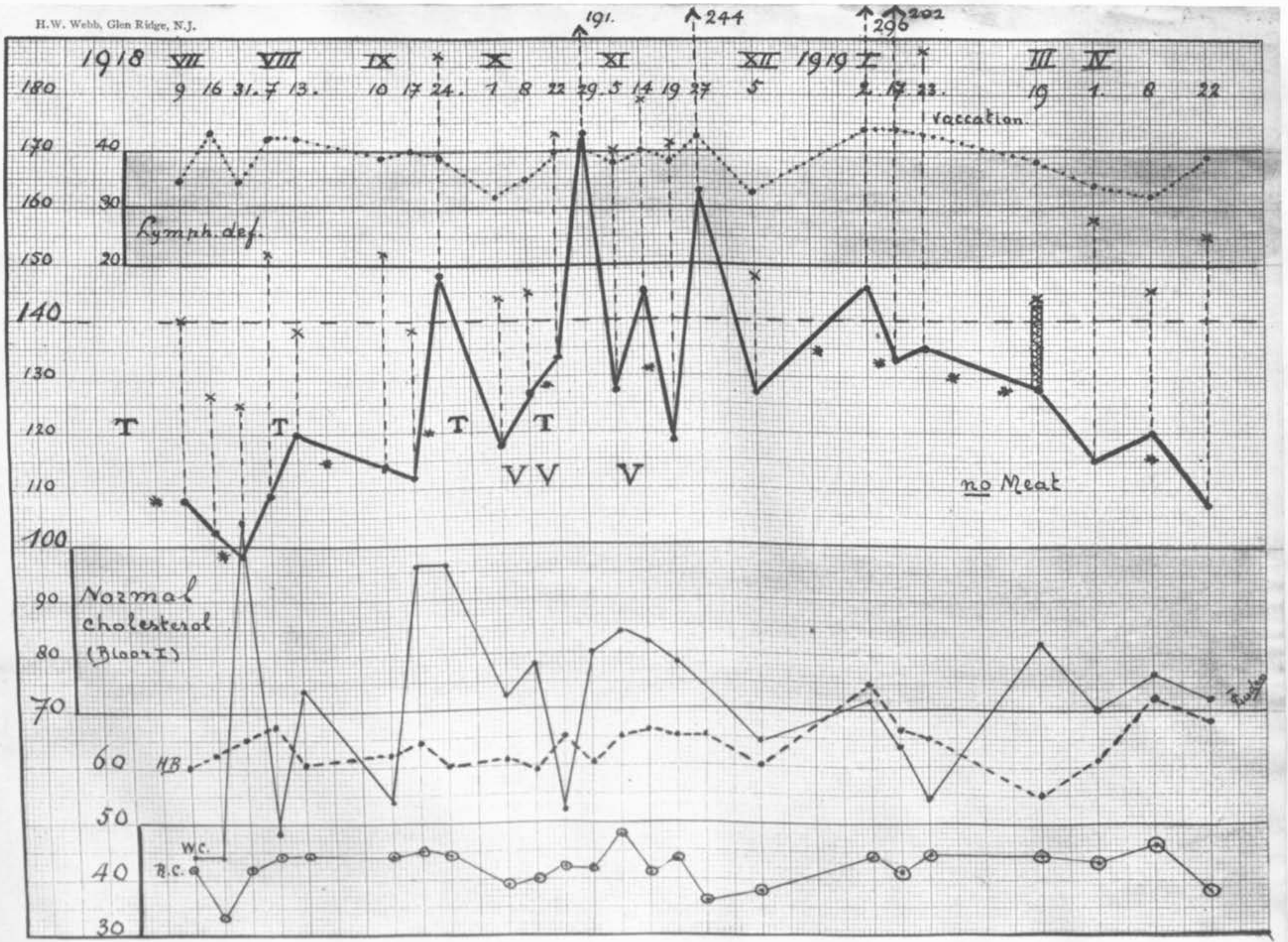


Fig. BII.

Fig. BII

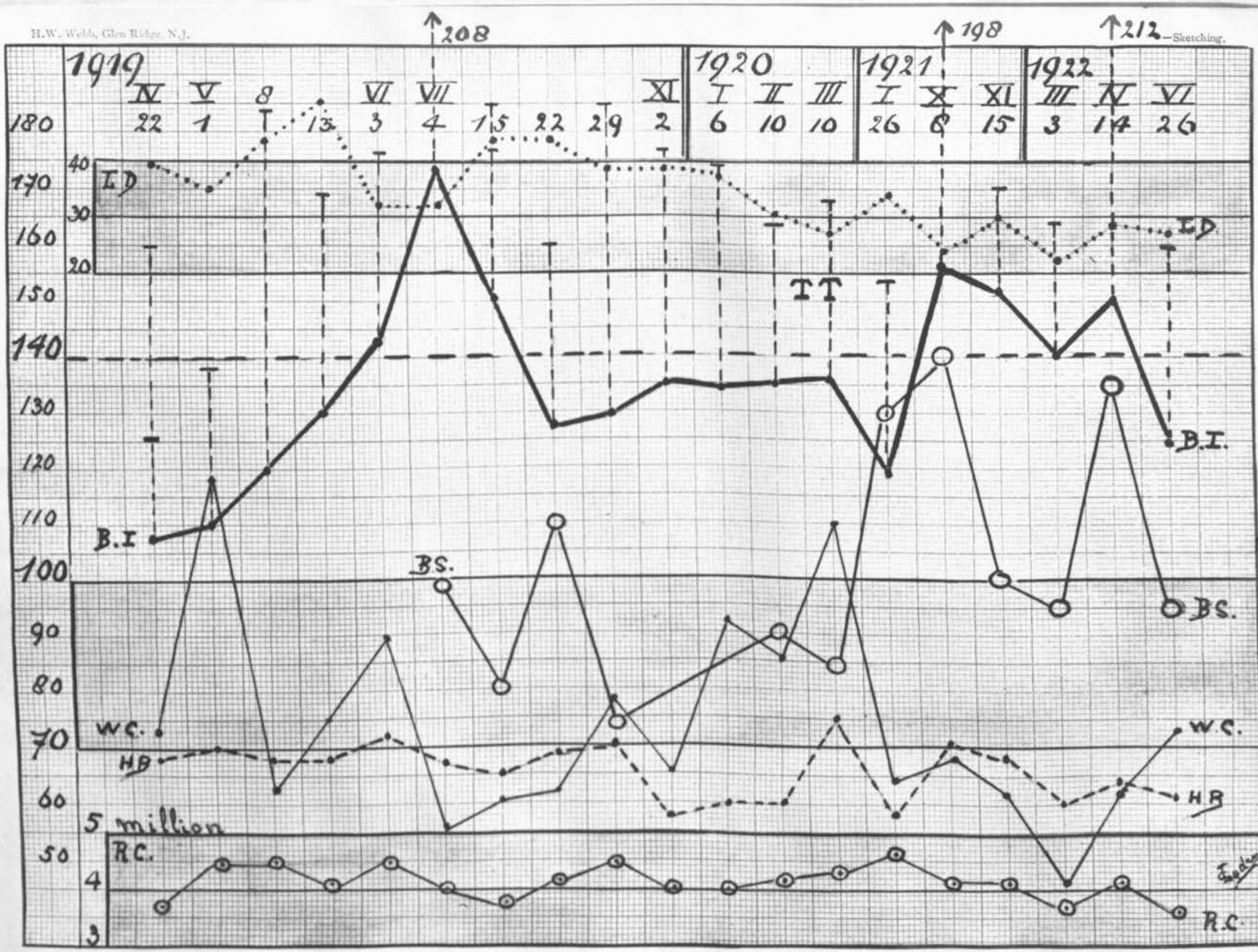
Fig. 34.



H.W. Webb, Glen Ridge, N.J.
1918
VII
VIII
IX
X
XI
XII
1919
I
III
IV
9 16 31. 7 13. 10 17 24. 7 8 22 29. 5 14 19 27 5 2. 17. 23. 19 1. 8 22
191.
244
296
202
Vaccation.
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
Lymph. def.
T
V
no Meat
Normal
cholesterol
(Bloor I)
HB
W.C.
R.C.

BIII

Fig. 35.


H.W. Webb, Glen Ridge, N.J.
Sketching.
208
198
212
1919
1920
1921
1922
IV V 8 VI VII XI
22 1 13 3 4 15 22 29 2
I II III
6 10 10
I X XI
26 8 15
III IV VI
3 14 26
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
5 million
4
3
I.D.
B.I.
BS.
W.C.
HB
R.C.

BIV

Fig. 36.

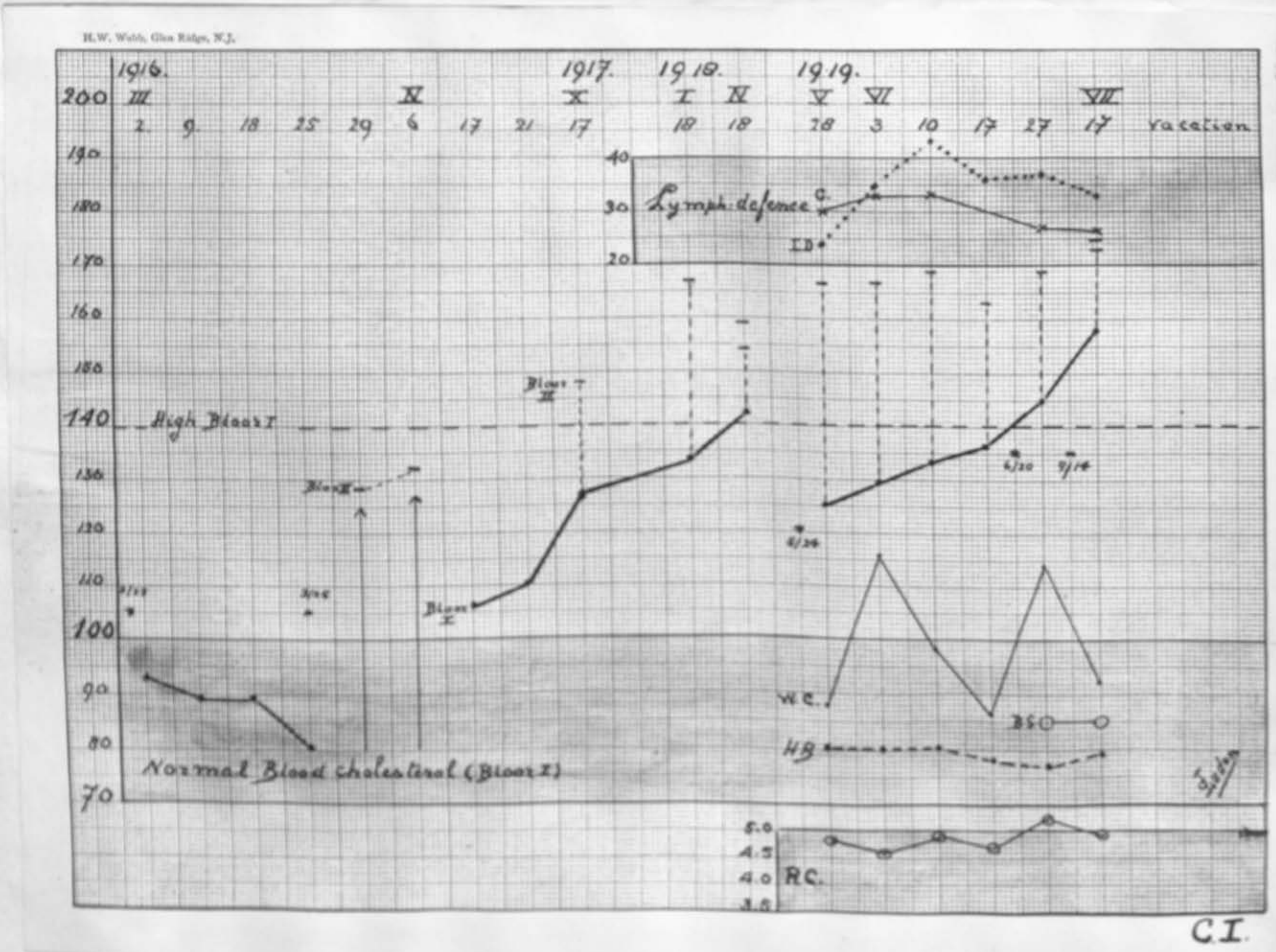

H.W. Webb, Glen Ridge, N.J.
1916.
1917.
1918.
1919.
vacation
High Blood I
Lymph defence
Normal Blood cholesterol (Blood I)
W.C.
HB
RC.
BS
C.I.

Fig. 37.

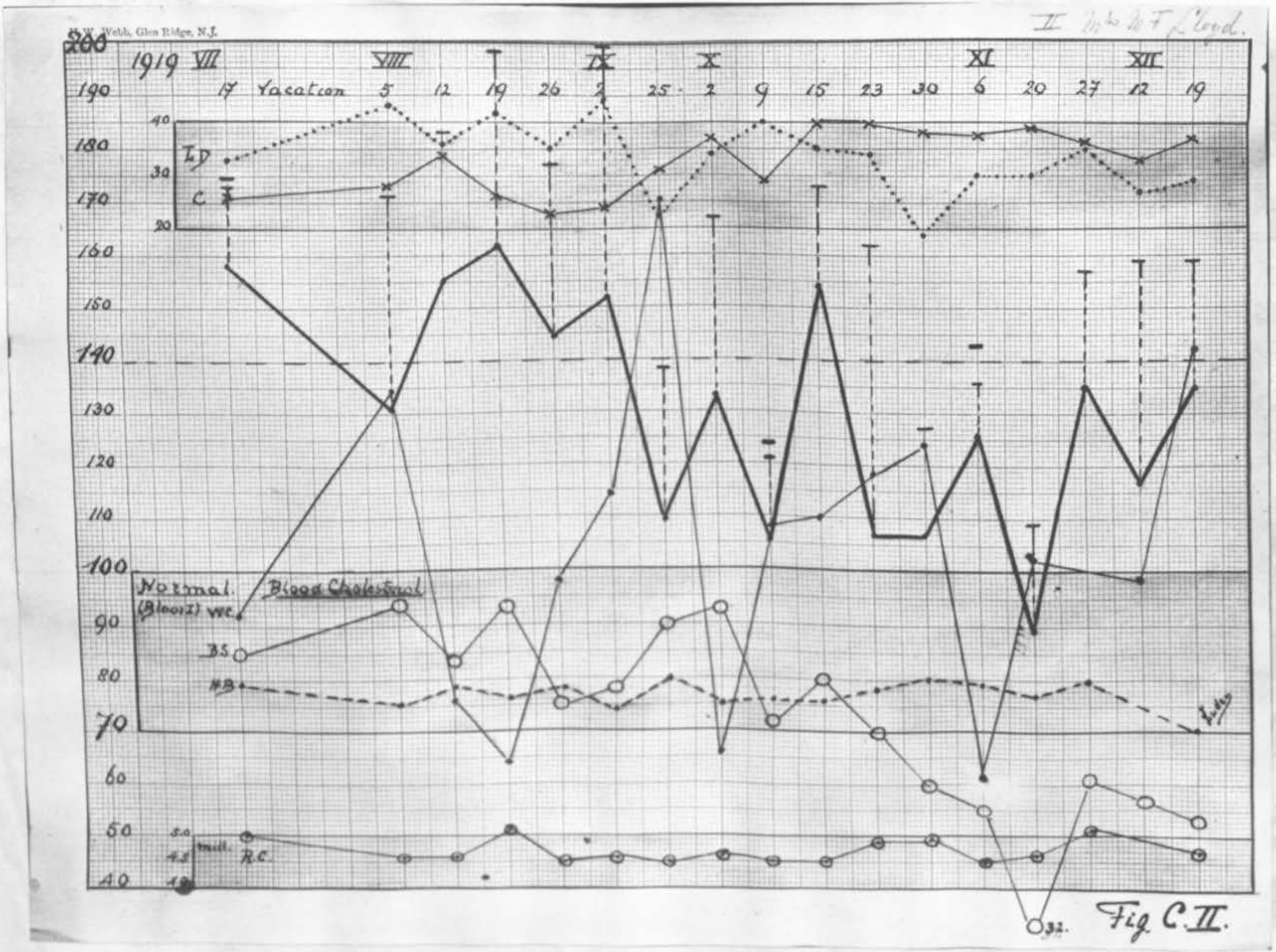
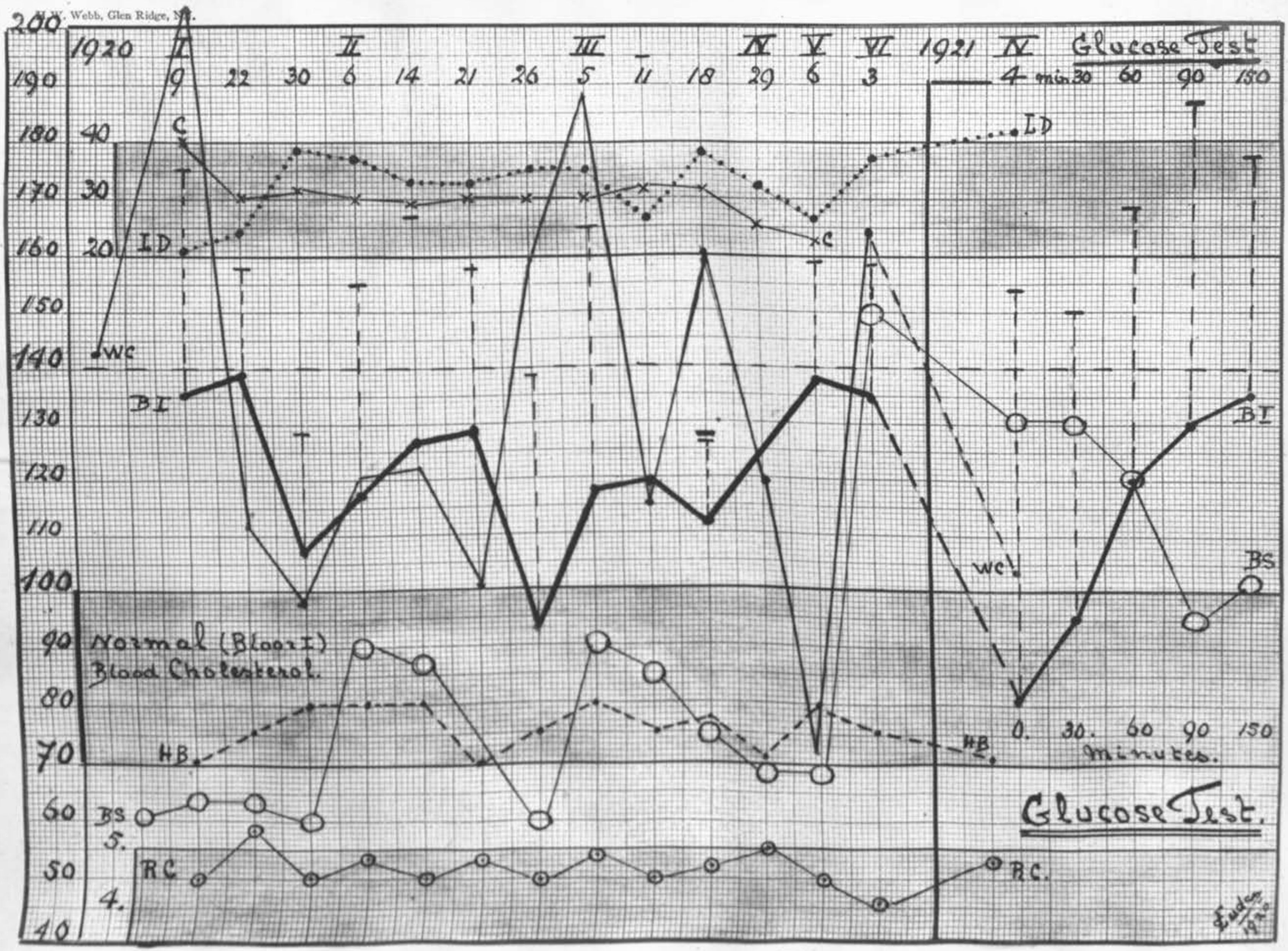

H. W. Webb, Glen Ridge, N.J.
II Mrs. M. F. Lloyd.
1919 VII
17 Vacation
VIII 5 12 19 26
IX 2 25
X 2 9 15 23 30
XI 6 20 27
XII 12 19
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40
40 30 20
I.D.
C
Normal. (Blood) W.C.
Blood Cholesterol
B.S.
H.B.
5.0 4.5 4.0
mill. R.C.
32.
Fig. C. II.

Fig. 38.



W. Webb, Glen Ridge, N.J.
1920
1921
Glucose Test
Normal (Blood I)
Blood Cholesterol.
minutes.
Glucose Test.
BI
BS
HB
RC
LD
WC
C

C. III

Fig. 39.

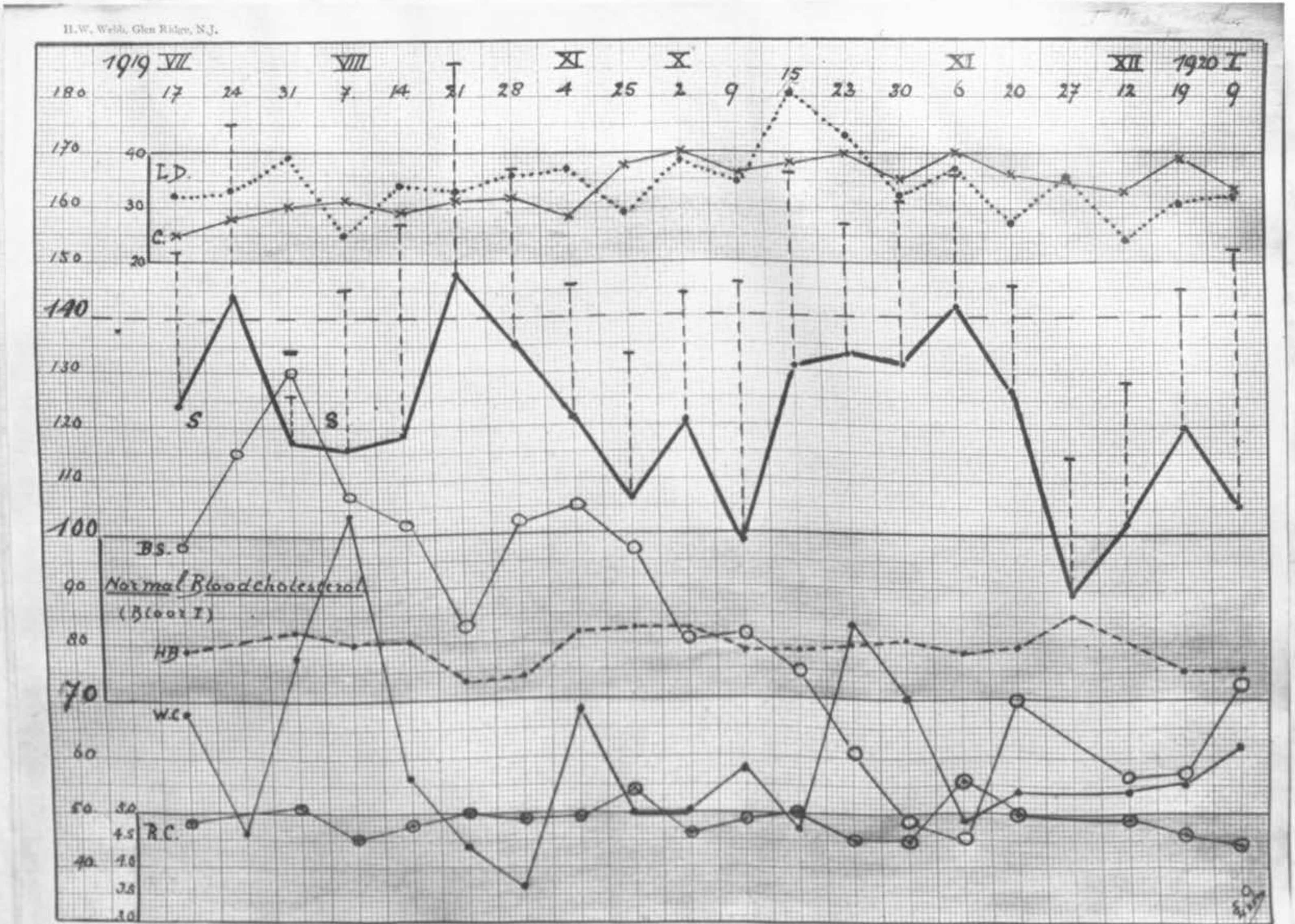

H.W. Webb, Glen Ridge, N.J.
1919 VII
17 24 31
VIII
7 14 21 28
XI
4 25
X
2 9 15 23 30
XI
6 20 27
XII
12 19
1920 I
9
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
L.D.
C.
40
30
20
S
S
B.S.
Normal Bloodcholesterol
(Bloor I)
H.B.
W.C.
R.C.
5.0
4.5
4.0
3.5
3.0

Fig D.I.

Fig. 40.

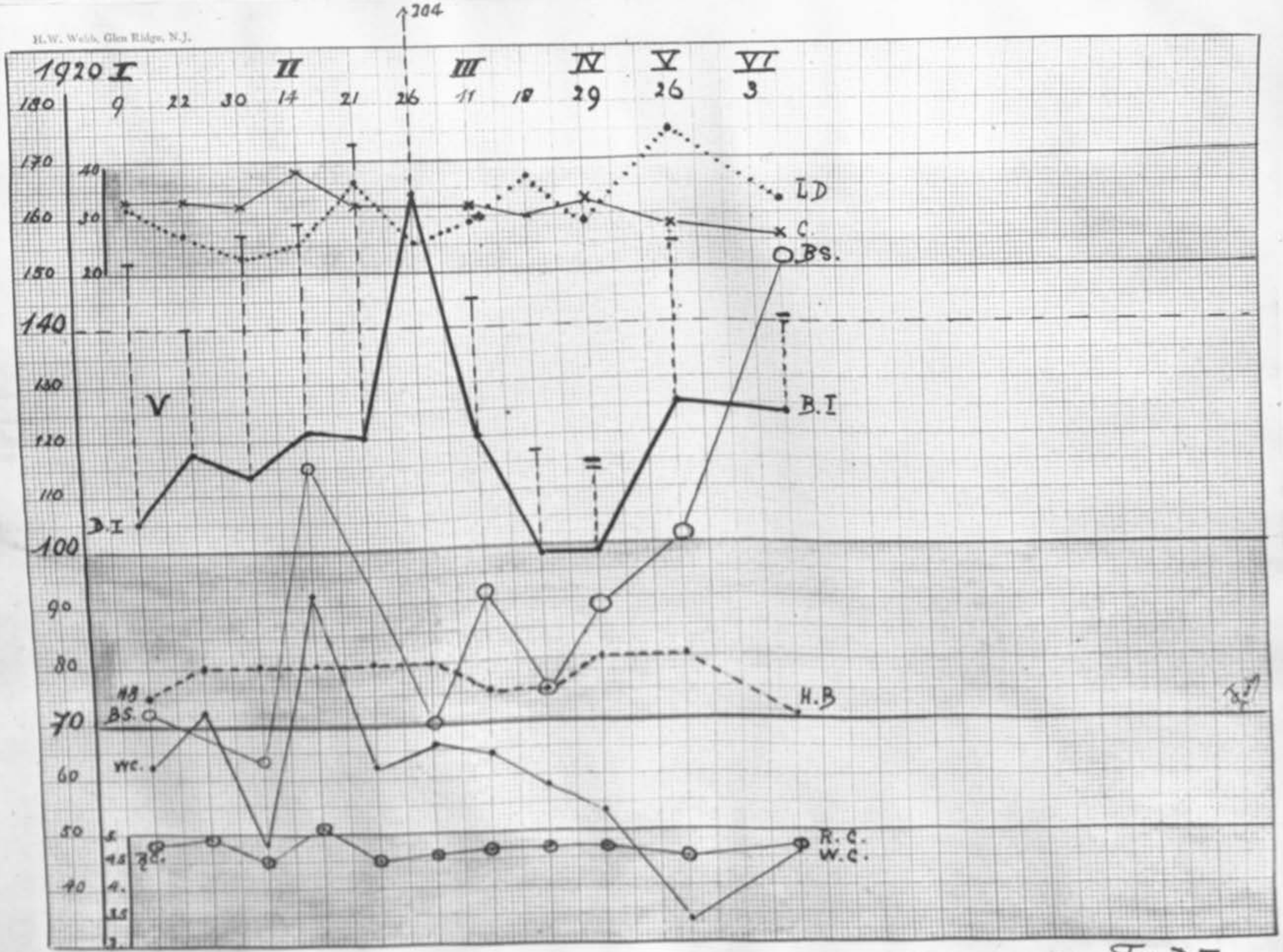
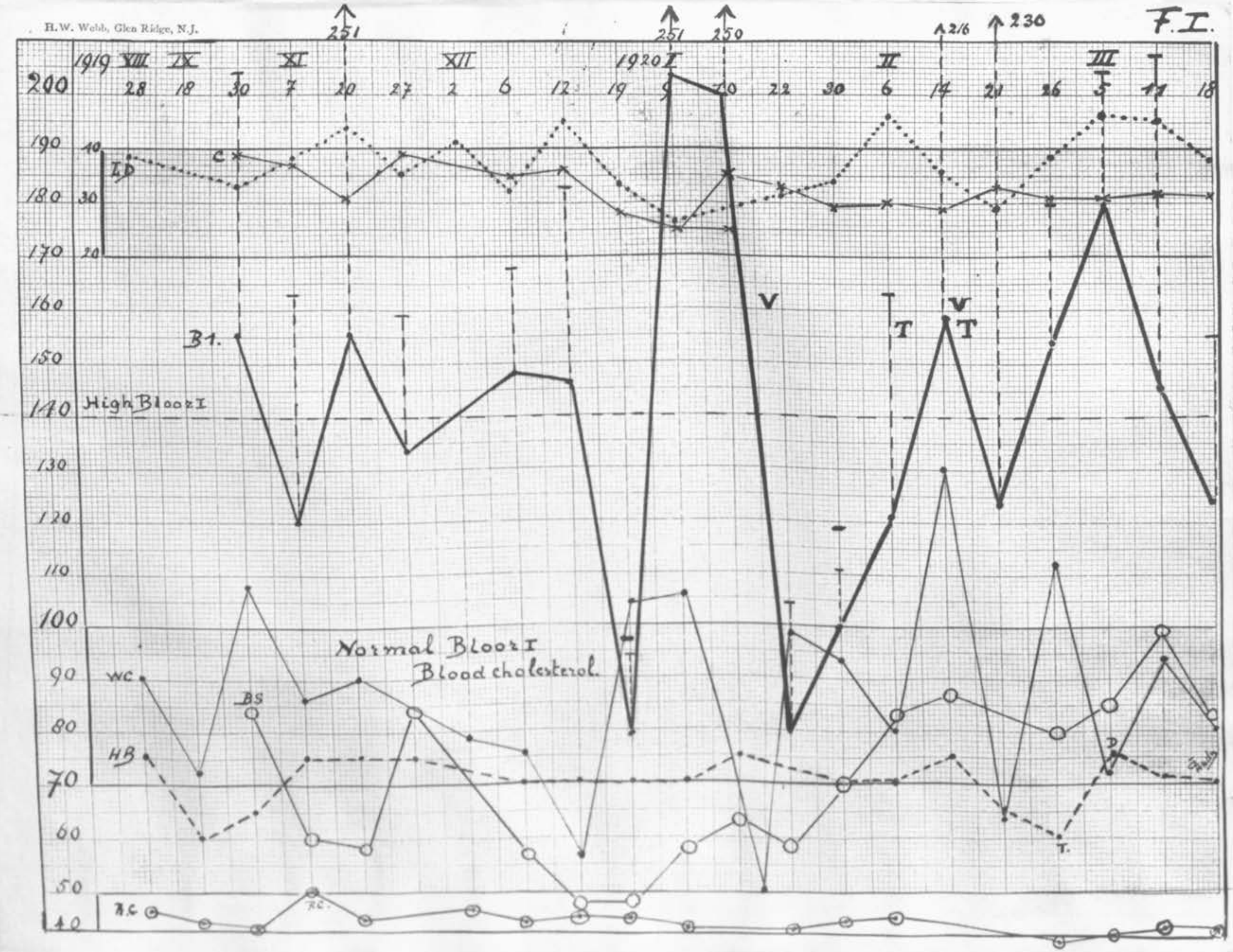


Fig. D II.

Fig. 41.



R.W. Webb, Glen Ridge, N.J.
F. I.
1919 VIII IX XI XII 1920 I II III
28 18 30 7 20 27 2 6 12 19 9 10 22 30 6 14 21 26 5 11 18
251
251
250
216
230
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ID
C
Bl.
High Blood I
V
T
Normal Blood I
Blood cholesterol.
WC
BS
HB
RC
D
T.

Fig. 42.

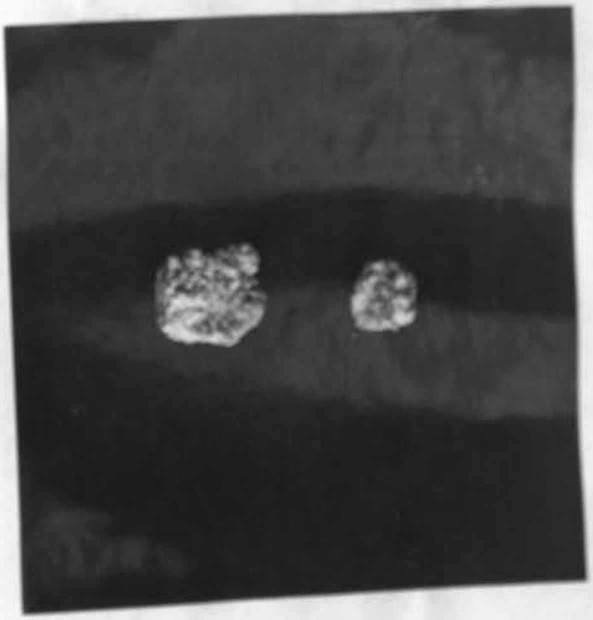
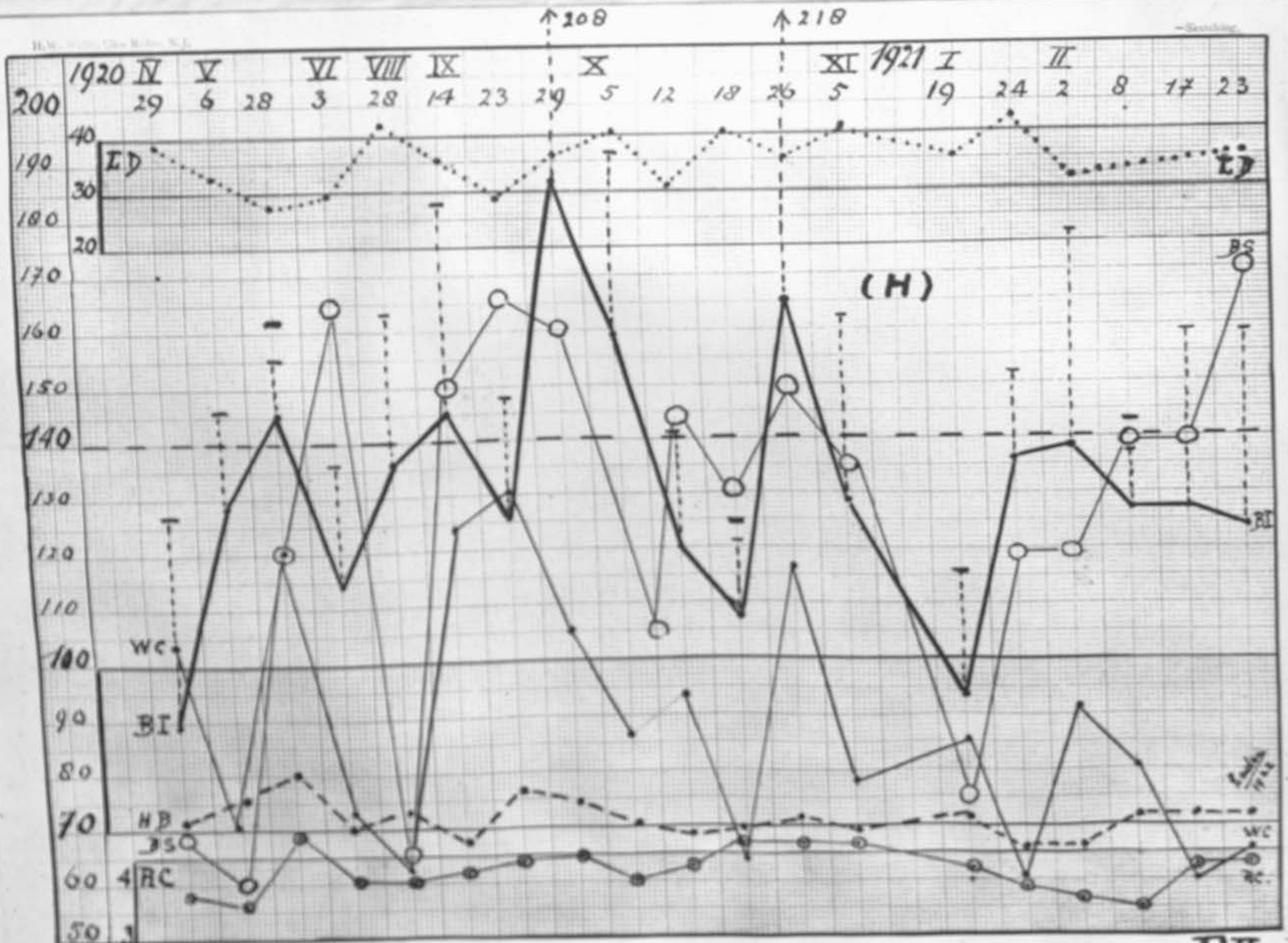


Fig. 42a.

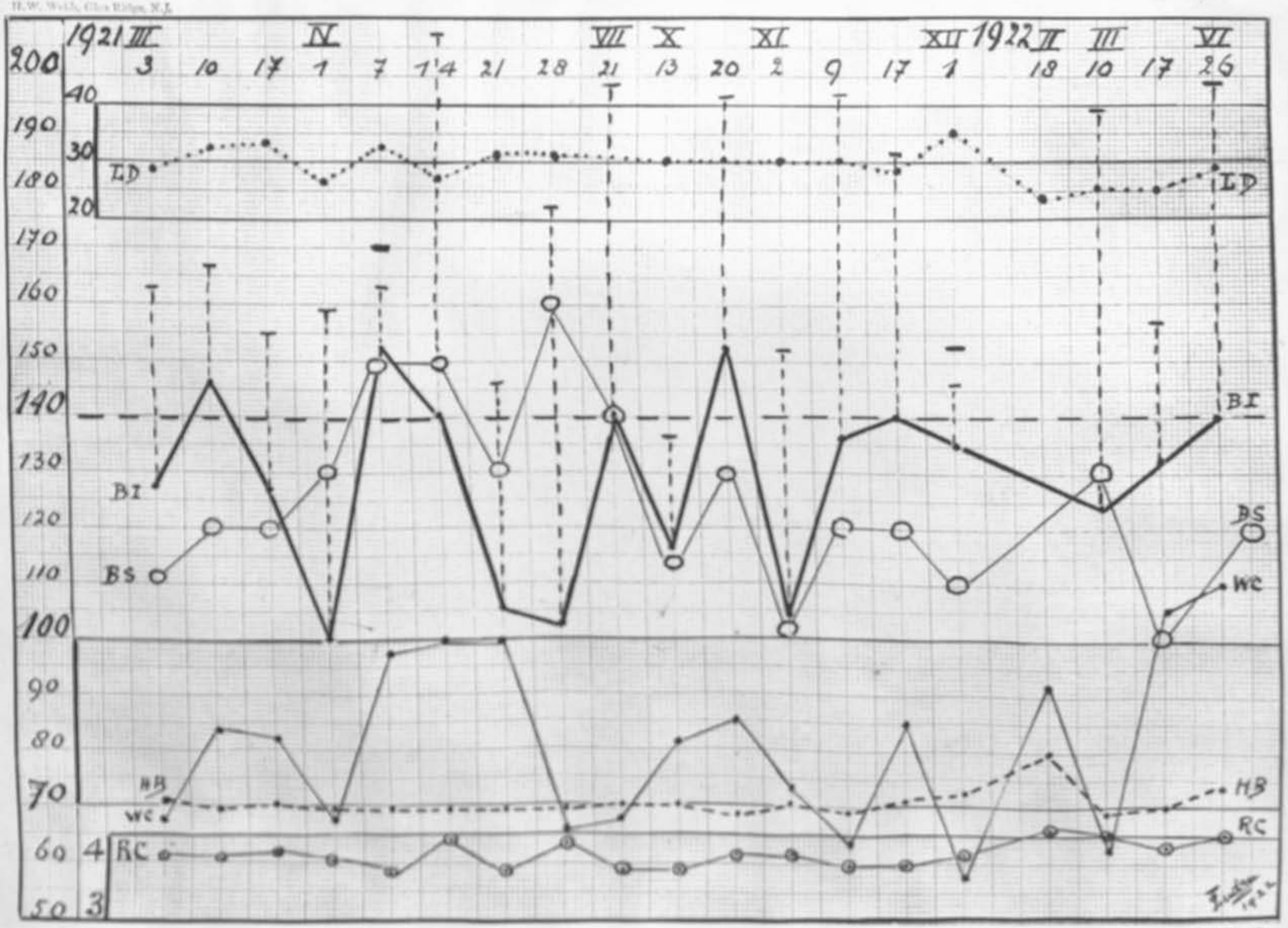


↑208
↑218
1920 IV V VI VIII IX X XI 1921 I II
29 6 28 3 28 14 23 29 5 12 18 26 5 19 24 2 8 17 23
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
LD
(H)
BS
BI
WC
HB
RC

FII

Fig. 43.

H. W. Webb, Glen Ridge, N.J.



F. III

FIG. 44.

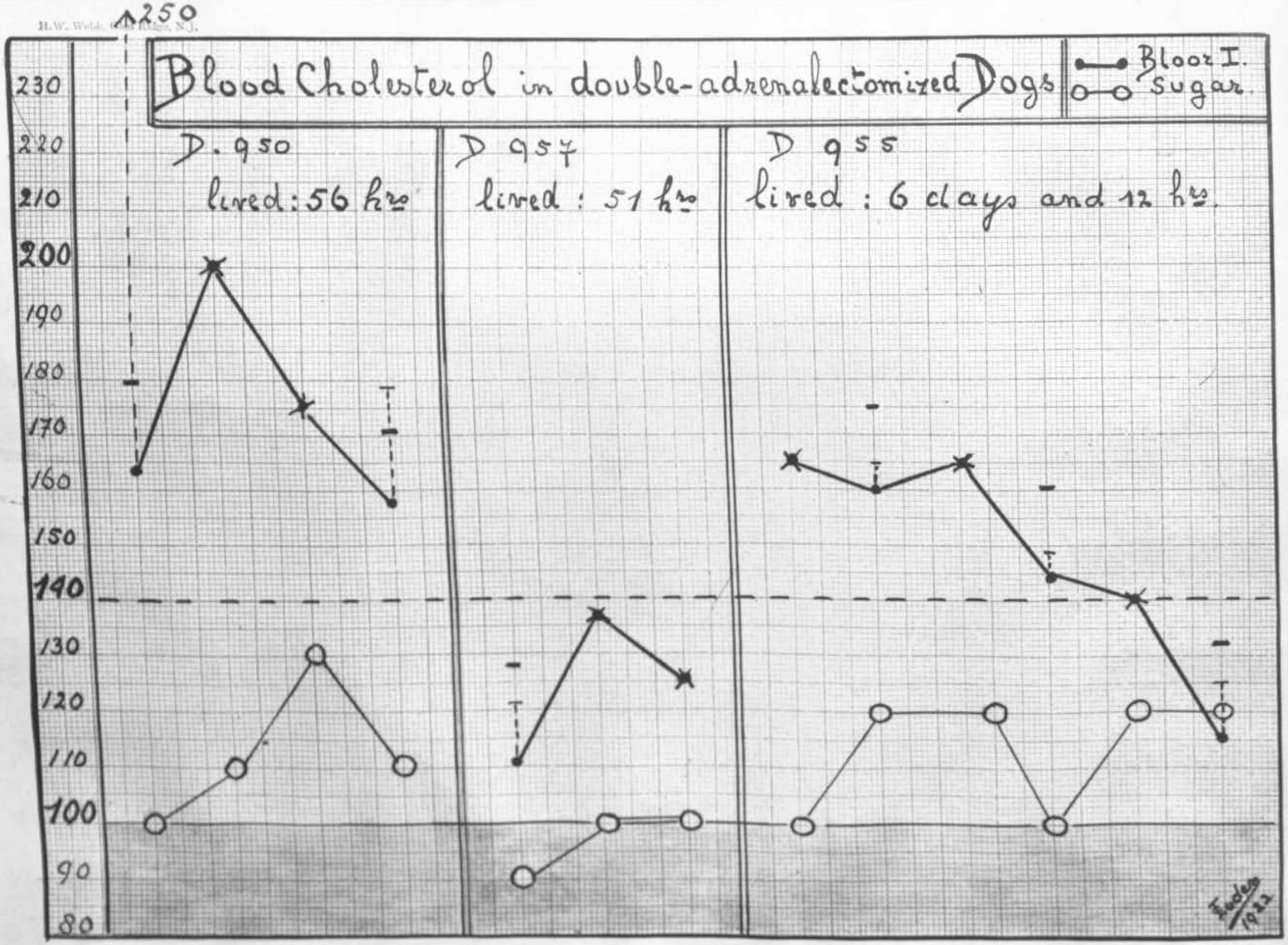

Blood Cholesterol in double-adrenalectomized Dogs
Bloor I.
sugar.
D. 950
lived: 56 hrs
D 957
lived: 51 hrs
D 955
lived: 6 days and 12 hrs.
250
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
1922

Fig. 45.

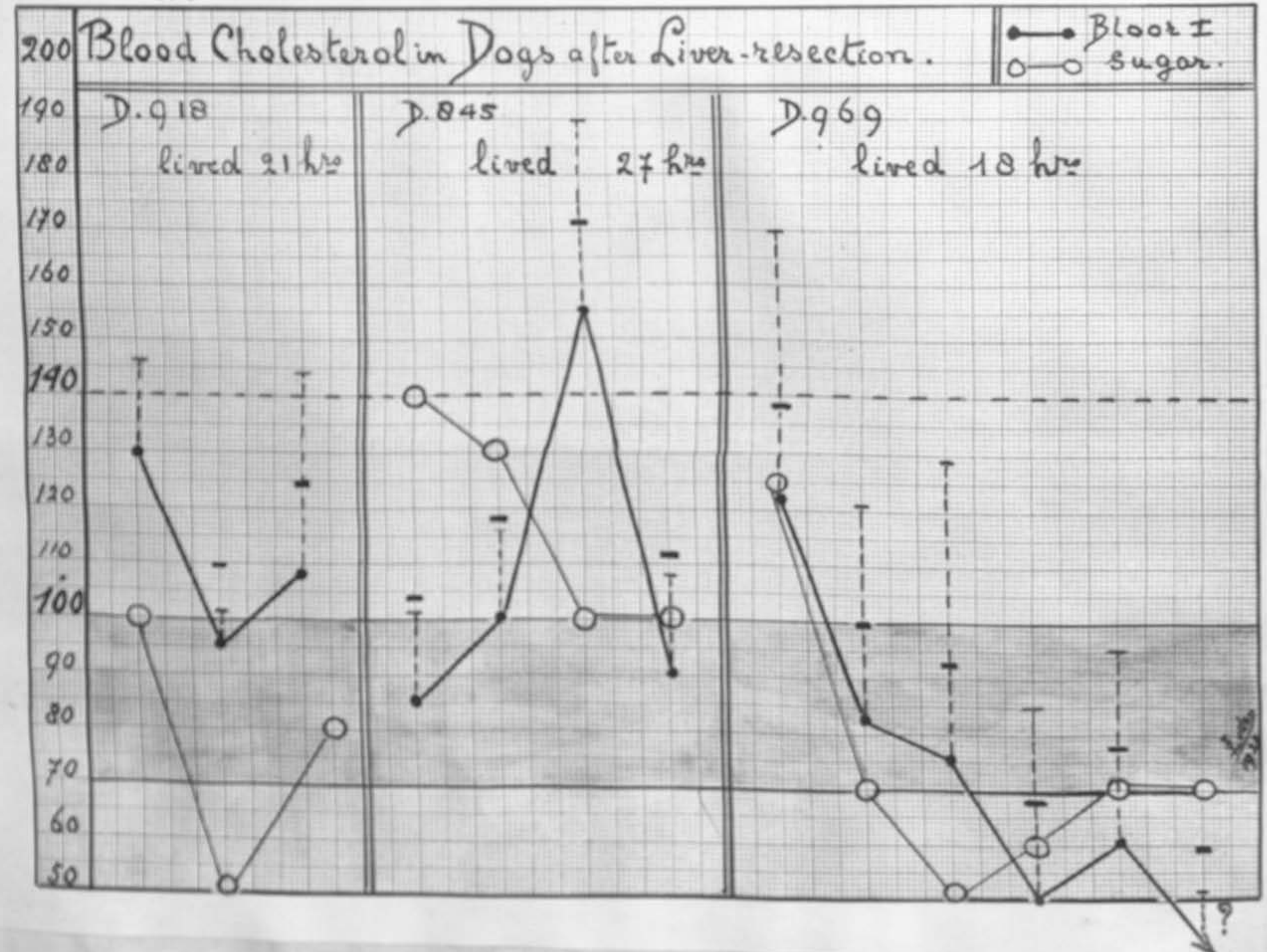

Blood Cholesterol in Dogs after Liver-resection.
Blood I
Sugar.
D.918
lived 21 hrs
D.845
lived 27 hrs
D.969
lived 18 hrs
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50

Fig. 46.

Legends

Fig. 22. Key to diagrams of blood constituents in Figures 23 to 42.

Fig. 23. Diagram of observations on constituents of the blood of A (the writer) during experimental diets, from November 23, 1915 to December, 1916. (AI) All determinations were made on blood samples taken before breakfast; both blood counts and chemical tests.

Fig. 24. Diagram of constituents of the blood of A from July 21 to December 18, 1917 (A II). Note the tendency to an inverse relation between the Bloor I blood cholesterol values (heavy solid line) and the total leukocyte counts (W.C., thin line) for which cell destruction alone does not account, as a great drop of the leukocytes is not always followed by a marked rise of the Bloor I values.

Fig. 25. Diagram of the constituents of the blood of A from January 3, to June 25, 1918 (A III). Note the same tendency to inverse relation between Bloor I cholesterol values and total leukocyte counts found in Figure 24, and the marked rise of the leukocytes up to 20,000 after experimental ingestion of 6 mg. of thyroxin (T) and the accompanying drop of the Bloor I values on April 16, but the rise of the blood cholesterol which is marked in the entries following June 29.

Fig. 26. Diagram of constituents of the blood of A from July 9, 1918, to March 1, 1919 (A IV). Note the continued tendency to an inverse relation between Bloor I cholesterol values and total leukocyte counts also shown in Figures 24 and 25, and the marked rise of the Bloor I values following injections of a prophylactic vaccine against influenza (V); A did not contract influenza during the epidemic prevailing in Rochester, Minnesota at that time, although repeatedly exposed to infection and although a pure culture of Pfeiffer bacilli was obtained from her nasopharynx April 6, 1919.

Fig. 26 a. Small, endothelium-lined cyst, resulting from the fifth injection of prophylactic vaccine, January 23, 1919. The cyst was excised from the writer's left arm April 11, 1919. The sections were accidentally destroyed before a photomicrograph had been made.

Fig. 27. Diagram of the constituents of the blood of A from March 1, to July 31, 1919 (A V). Note the high level of the total leukocyte counts, which is more marked than in Figure 26 and ranges around 20,000 to 22,000. The explanation of these high leukocyte counts was found several months later (October 25, 1919); they were caused in all probability by slow chronic carbon monoxid poisoning from a defective hot water heating system, as A did not suffer from any inflammatory or infectious condition during this period and as a leukocytosis is known to be produced by carbon monoxid poisoning. Blood sugar determinations begun.

Fig. 28. Diagram of the blood constituents of A during the entire year 1919 (A V2), showing the effect of experimental ingestion of total dessicated suprarenal. Each of the hatched blocks indicates a "suprarenal experiment"; 1200 mg. of the dried gland were taken in five days during the first, 1200 mg. in six days during the second experiment; 2000 mg. in nine days during the third, and 200 mg. in one day during the last (control) experiment. The solid black block indicates the experimental ingestion of 1 mg. of thyroxin. A definite change in the behavior of the blood constituents may be seen by comparing the right half of the diagram (January to July, 1919) with the left half (August to December, 1919); the changes in the composition of the blood are discussed under seven headings in the text, pages 211 to 214, Part III.

Fig. 29. Diagram of the constituents of the blood of A from August 1 to December 19, 1919 (A VI). Note the very low blood sugar values, 0.040 per cent, and coincident leukocyte count of 20,000 on October 30, five days after A discovered the defective furnace by going into the cellar, with resulting marked

symptoms of carbon monoxid poisoning; a similar drop of the blood sugar values was found in the blood of three other persons (B, C, and F) who, being in the house of A, were also exposed to the odorless furnace gas. Note also the high Bloor I blood cholesterol value on August 5, during a period of prevalent influenza-like "colds" in Rochester, Minnesota; A again remained immune, and marked changes in the blood cholesterol of three other persons (Figs. 36, 38, and 40) were observed between August 5 and August 21, 1919.

Fig. 30. Diagram of the constituents of the blood of A from January 1 to September 29, 1920 (A VII). Note the sharp rise in the Bloor I cholesterol values February 14, during the influenza epidemic in Rochester, Minnesota in January and February, 1920. A had an injection of prophylactic vaccine against influenza (V) January 10, followed by a drop of the blood cholesterol, but again did not contract influenza although in intimate contact with patients suffering from influenza. Similar marked changes in the blood cholesterol were found in three other persons (Figs. 38, 40, and 42).

Fig. 31. Diagram of constituents of the blood of A from October 5, 1920 to April 28, 1921 (A VIII). Note low blood sugar value October 18, 0.070 per cent, and sharp rises of total leukocytes, to 22,000 and 24,000, February 2 and 17, 1921. According to A's records in day-logue symptoms of slight carbon monoxid poisoning, (scalp headache, nausea, numb face and feet, black narrow veins) were observed October 14, 1920 after smoke from neighboring chimney filled A's house, while special mention is made of much exhaust in town, and odor of gas in a friend's house January 20, 1921 and February 11, 1921. Both blood sugar determinations and blood counts given in all the diagrams have been made by A's assistants, who never saw A's records: all personal equation is thus eliminated.

Fig. 32. Diagram of constituents of the blood of A from July 21, 1921 to June 26, 1922 (A IX). Fewer determinations were made during this period on account of A's absence from Rochester. Note the lower range of the

total leukocytes, which is of interest as a possible indication of exhaustion of the leukocytic reaction because of exposure to illuminating gas, by bad leak in laboratory gas fittings of water bath November 3, 1921, is followed only by a rise to 14,000 November 17, 1921; the odor of gas had been noticed for several days but the leak had proved difficult to find. Details in Chapter XII.

Fig. 33. Diagram of the constituents of the blood of B from July 21 to December 18, 1917 (B I). Halsted operation for highly malignant type of cancer of left breast July 5, 1917; microscopic diagnosis: recurrence expected within a year. Note the still high (over 140 mg.) Bloor I cholesterol values July 21, and gradual reduction of Bloor I values during following months with marked increase of split cholesterol values. Therapy: meatless diet, roentgen ray (one exposure) and radium. Observe reduction of split cholesterol immediately after x-ray (crossed dot, August 21) and far greater reduction of Bloor I values accompanied by far greater increase of split cholesterol following radium treatments (R). Note also low general level of total leukocytes (below 6000) but good values of "lymph defence", average 30 per cent and higher. Patient free from recurrence August, 1922.

Fig. 34. Diagram of the constituents of the blood of B from January 3 to June 25, 1918 (B II) (Halsted operation July 5, 1917). Note further reduction of Bloor I cholesterol values with accompanying large amounts of split cholesterol under administration of small doses of thyroxin (T); consistent low level of total leukocytes (W.C.) but good high level of "lymphoid defence".

Fig. 35. Diagram of the constituents of the blood of B from July 9, 1918 to April 22, 1919 (B III). Note reduction of Bloor I values by thyroxin (T), sudden rise following injection of prophylactic vaccine (V) during influenza epidemic in Rochester, Minnesota, and subsequent reduction of Bloor I values by dietary measures (no meat). B remained immune from influenza; for comparison see Figure 26. Note also the rather higher level of the total leukocyte

counts during the epidemic, the tendency to inverse relation between leukocytes and Bloor I cholesterol which is less marked than in Figures 23 to 30, A I-VII, and the consistent good, high level of the "lymphoid defence".

Fig. 36. Diagram of the constituents of the blood of B from April 22, 1919 to June 26, 1922 (B IV). Note the sharp rise of the Bloor I blood cholesterol values July 4, during the epidemic of influenza-like "summer colds" in Rochester, Minnesota. B did not contract the prevalent infection; for comparison see Figures 29, 38, and 40. The relatively smaller number of determinations in 1920, 1921 and 1922 shows a tendency to higher Bloor I cholesterol values, but satisfactory amounts of split cholesterol (vertical broken bars); the blood sugar values have risen; the lymphoid defence is satisfactory though not as high as in previous years. The patient continues to be in good health; the presence in her home of a gas range of which the odor is often noticeable is a factor which may play a part in the somewhat less satisfactory findings during the latter years. The general trend of curves of the blood constituents is being carefully watched for this reason.

Fig. 37. Diagram of the constituents of the blood of C from March, 1916 to July 16, 1919 (C I). C in good health (control); had cholecystectomy January, 1915. Note the gradual rise of Bloor I cholesterol values in 1919, with coincident rise of lymphoid defence. (The first four entries in 1916 are determinations by Autenrith method giving lower values than Bloor's).

Fig. 38. Diagram of the constituents of the blood of C from July 17 to December 19, 1919 (C II). Note the tendency to inverse relation between Bloor I cholesterol values and total leukocyte counts; rise of Bloor I in August, 1919 during period of influenza-like "colds"; and very low blood sugar values (0.032 per cent) November 20; C spent a great deal of time at the house of A during the production of carbon monoxid by A's defective furnace and a defective furnace was also detected in her own house.

Fig. 39. Diagram of the constituents of the blood of C from January 1, 1920 to June 3, 1921 (C III). Note continued tendency to inverse relation between Bloor I values and total leukocyte counts; persistent low blood sugar values in the first four entries and on February 26, 1920 (0.06 per cent); various defects in the furnace of C's house only discovered and definitely remedied the first week in March. The last four entries, June 3, 1921, represent a sugar tolerance test; blood samples were taken at thirty minute intervals.

Fig. 40. Diagram of the constituents of the blood of D from July 17, 1919 to January 1, 1920 (D I). D in good health (control); husband of C and neighbor of A. Note tendency to inverse relation between Bloor I cholesterol values and total leukocyte counts, which have a low level (4000-7000); a sharp rise of the Bloor I cholesterol following experimental ingestion of 200 mg. desiccated total suprarenal substance (S), similar to findings in Figure 28, and the steady decrease of the blood sugar values, which seems connected with the production of carbon monoxid in D and C's house, as a very marked drop occurs November 6 (0.065 per cent) after D had been repeatedly in the furnace room of A's house to investigate matters for A; for comparison see Figure 29.

Fig. 41. Diagram of the constituents of the blood of D from January 9 to June 3, 1920 (D II). Note the continued tendency to low total leukocyte counts (7000-9000); sharp rise of the Bloor I cholesterol values February 26, which followed a recurrence of influenza February 20 and after which D's symptoms, intense headache, subacute sinusitis and marked injection and pain in the eyeballs, rapidly subsided. Note also the steady improvement in the blood sugar values, following final repairs in the furnace of D's house, eliminating the production of carbon monoxid.

Fig. 42. Diagram of the constituents of the blood of F from August 28, 1919 to March 18, 1920 (F I). F, an unmarried woman, aged thirty-three years, came to Rochester at the end of July, 1919; she almost immediately contracted

a severe form of the prevalent influenza-like "colds", in her case a typical influenza. She lived at the house of A and was very severely affected by the carbon monoxid from the defective furnace. The details of F's case are discussed in Chapter XII. Note the unusually high Bloor I values on January 9 and 10 during the epidemic of influenza in Rochester; the sharp rises of the Bloor I cholesterol February 14 and March 5 coincided with recurrences of influenza in F. Note also the very low blood sugar values (0.045 per cent) following the chronic carbon monoxid poisoning; for comparison see Figures 29, 30, 31, 32, 38, 39, 40 and 41.

Fig. 42 a. Disintegrated mortar removed with fingernail from the joints between the bricks in the chimney flue in house of F.

Fig. 43. Diagram of the constituents of the blood of F from April 29, 1920 to February 23, 1921 (F II). The clinical symptoms of F, March to December, 1920 were as varying as the curves in the diagram: severe menstrual disturbances and intense headaches dominated the picture. Features of importance in the clinical history were: rupture of the appendix at the age of seven, appendectomy twenty years later; numerous severe attacks of influenza; enucleation of the left breast for fibroadenoma; Kelly's operation for fixation of the left kidney; chronic carbon monoxid poisoning September to December, 1919. Exploration laparotomy, December 29, 1920 revealed complete fibrous and cystic degeneration of both ovaries with occlusion of tubes (microscopic: inflammatory changes, no trace of tuberculosis or malignancy); uterine myomas; sigmoid bound down by adhesions; details in Chapter XII. Subtotal hysterectomy (H) followed by rapid improvement of general health. Note the drop of Bloor I cholesterol values, gradual rise of blood sugar and lower level of total leukocyte counts after January 24, 1921. The persistently high lymphoid defence, and the satisfactory amounts of split cholesterol were considered indicative of inflammatory rather than malignant changes: assumption confirmed by laparotomy.

Fig. 44. Diagram of constituents of the blood of F from

March 3, 1921 to June 26, 1922 (F III). Observe the more even tenor of the curves. Note the still relatively high Bloor I cholesterol and blood sugar values, which are known to follow castration; the large amounts of split cholesterol and the lower level of the leukocyte counts. Patient enjoyed better health than she had for years.

Fig. 45. Diagram of blood cholesterol and blood sugar values in three dogs after double adrenalectomy. First entry: blood sample taken before removal of second suprarenal; the dogs had had only one suprarenal gland for about two weeks; the other blood samples were taken after removal of the second suprarenal; the dogs lived fifty-six, and fifty-one hours, and six days and twelve hours respectively. Note the reduction or total absence (crossed dot) of split cholesterol; the terminal increase of split cholesterol in the three last entries are probably the result of an increased metabolic rate caused by the death struggles of the animals.

Fig. 46. Diagram of blood cholesterol and blood sugar values in three dogs after resection of the liver. Note: contrast with Figure 43. The amounts of split cholesterol are large, falling but little below the normal minimum (17 mg.) as indicated by small thick bar on vertical broken line, although in Dog 969 the Bloor I values decreased markedly, being too low for accurate reading in the last determination (?). The dogs lived for twenty-one, twenty-seven and eighteen hours respectively.

Fig. 47.

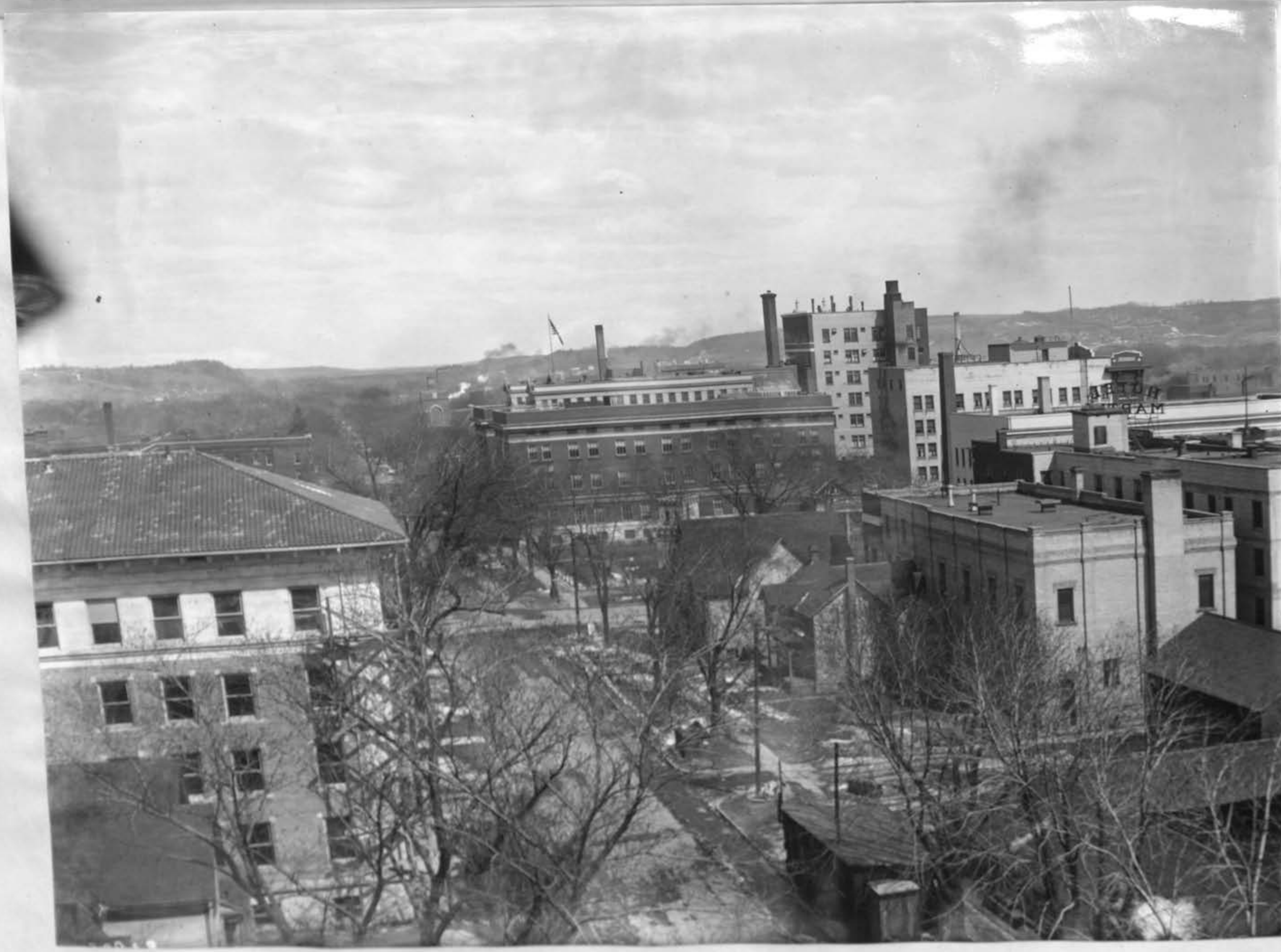
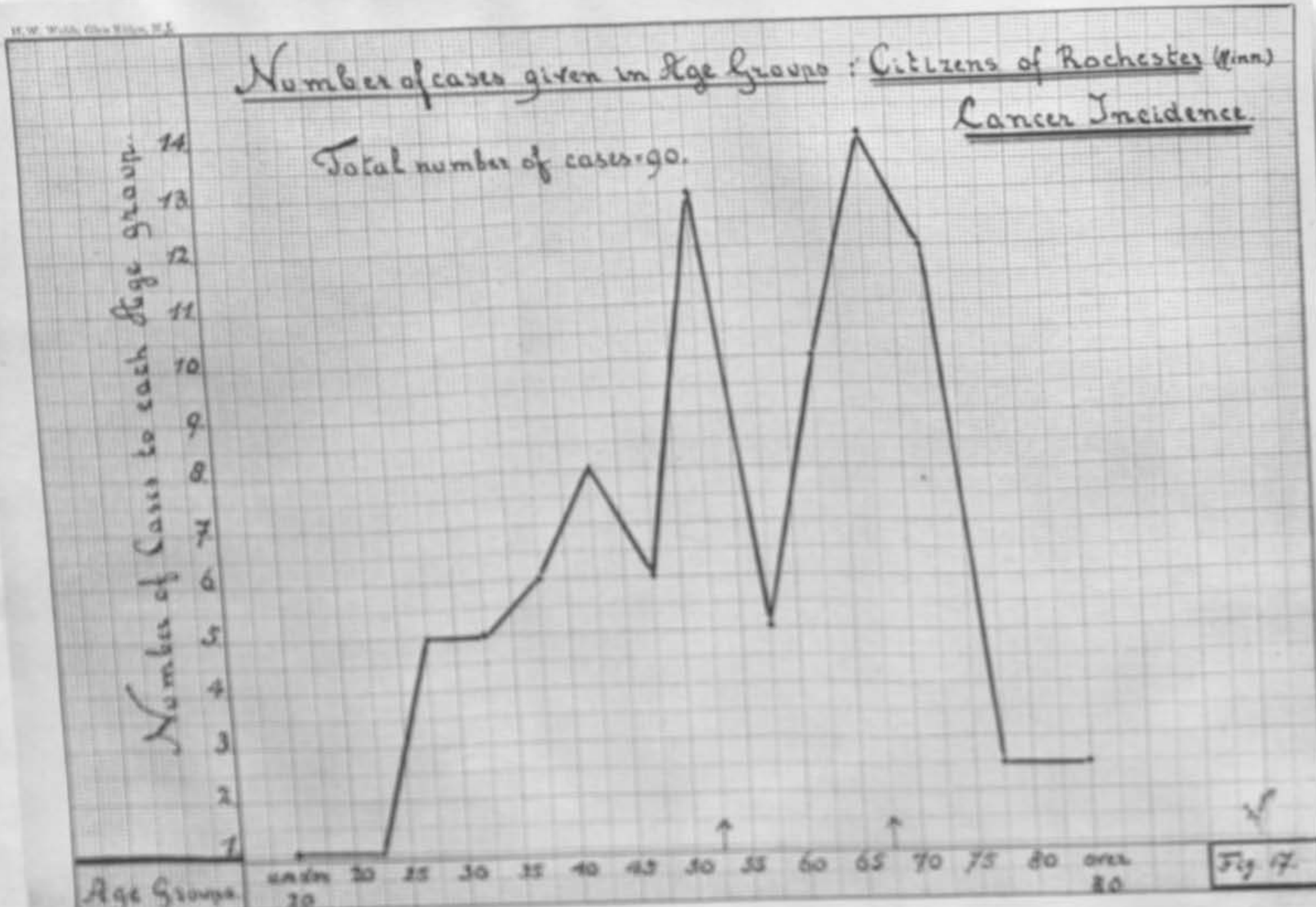


Fig. 48.

Fig. 49. City plan of Rochester, Minnesota, showing distribution and increase of large, smoke-producing buildings, 1914-1918. Buildings erected before 1914 marked in outline, buildings erected from 1914 to 1918 marked in solid black. Observe that the large buildings form a kind of barrier on the eastern side of the city, which impedes elimination of combustion products by prevailing Northwest winds, promoting retention of smoke and soot in the "cup" containing the main portion of the city.



Number of cases given in Age Groups : Citizens of Rochester (Minn)
Cancer Incidence.
Total number of cases = 90.
Number of Cases to each Age group.
14
13
12
11
10
9
8
7
6
5
4
3
2
1
Age Groups.
under 20
20
25
30
35
40
45
50
55
60
65
70
75
80
over 80

Fig. 17.

H.W. Webb, Glen Ridge, N.J.

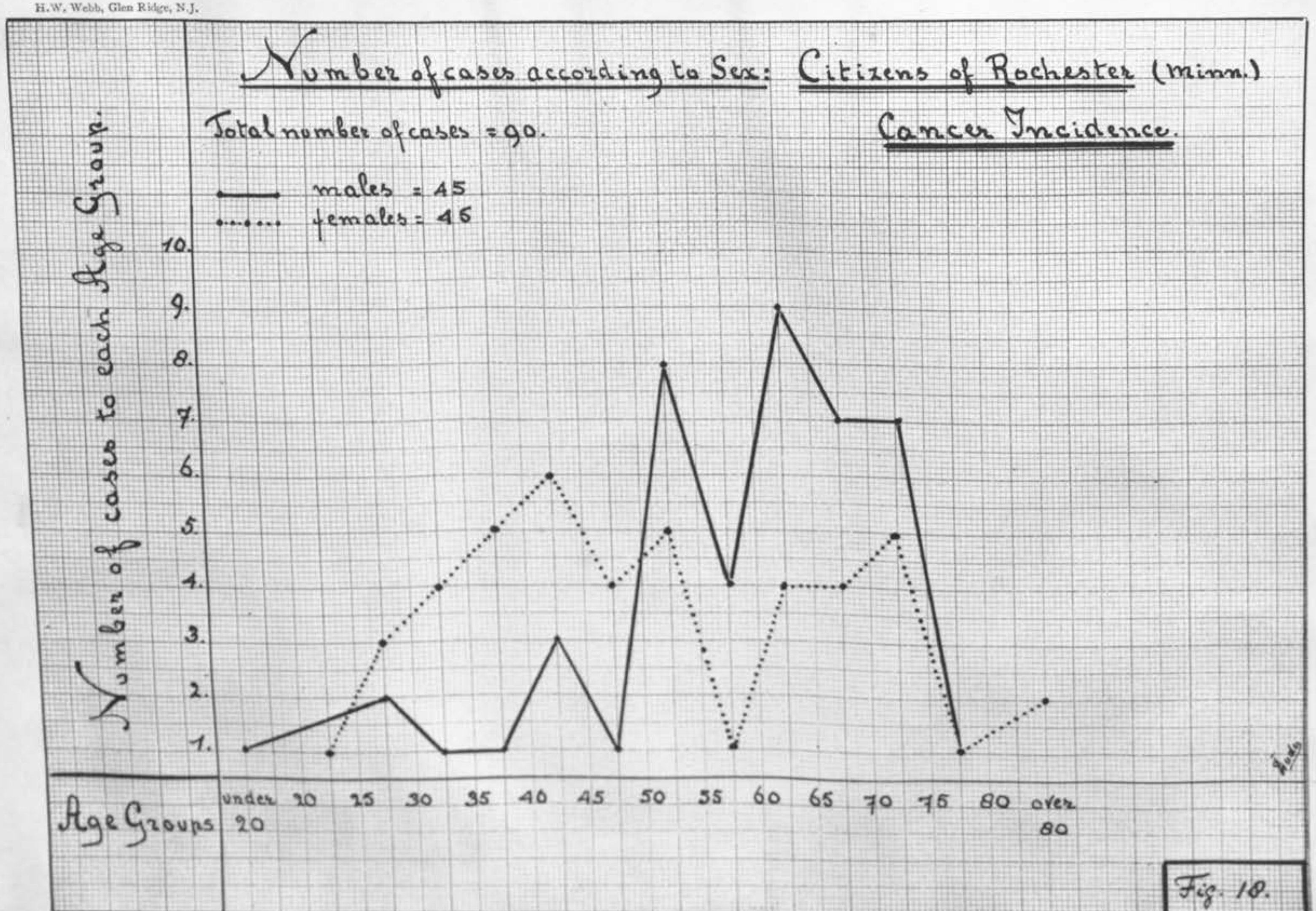


Fig. 18.

Fig. 51.

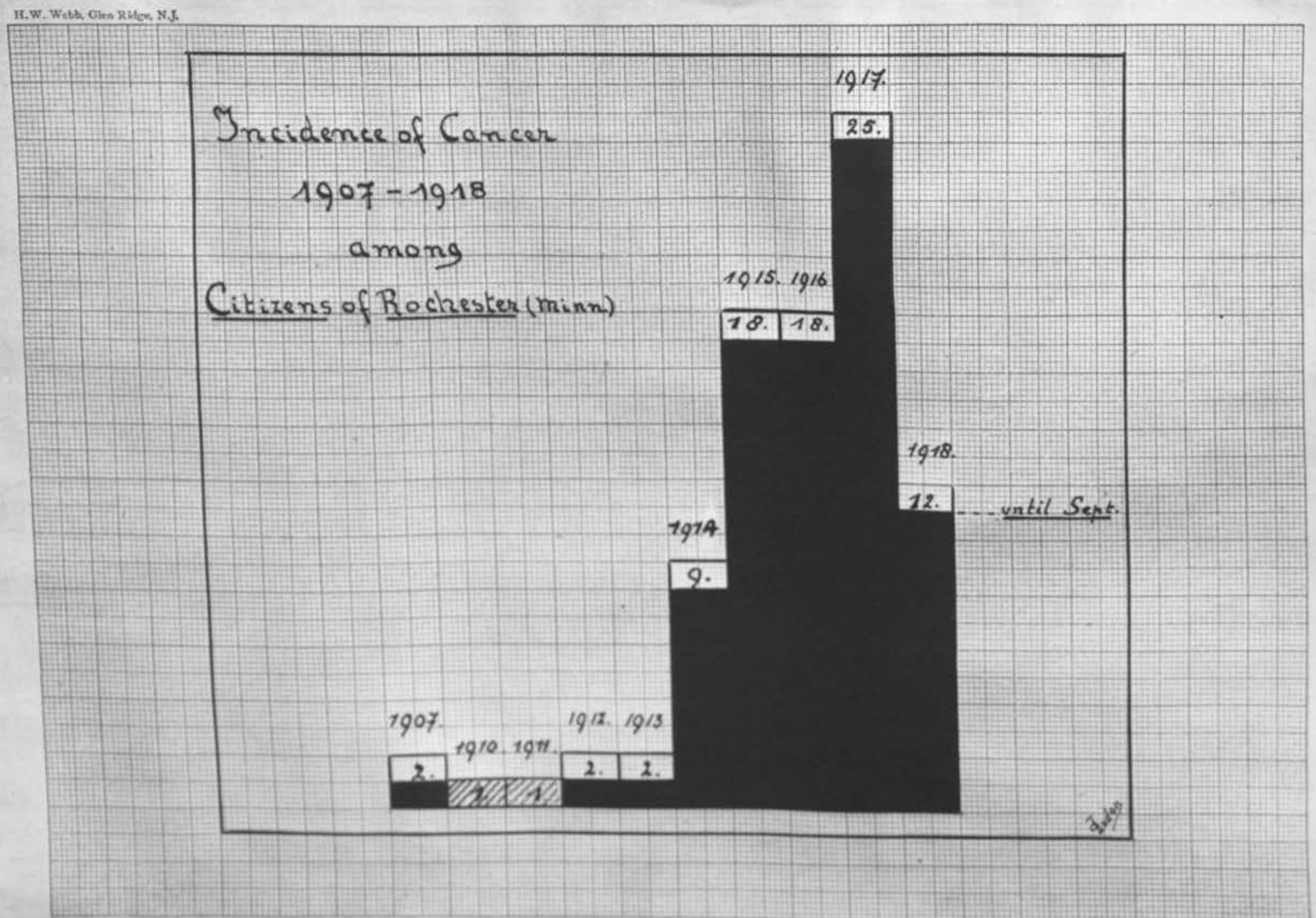

H.W. Webb, Glen Ridge, N.J.
Incidence of Cancer
1907 - 1918
among
Citizens of Rochester (Minn)
1907.
2.
1910. 1911.
1
1
1912. 1913
2.
2.
1914
9.
1915. 1916
18.
18.
1917.
25.
1918.
12.
until Sept.

Fig. 19.

Fig. 52.


MAP OF
ROCHESTER, MINN.
CHURCHES
SCHOOLS
SUBDIVISION
SECTION
ADDITION

Fig. 53.

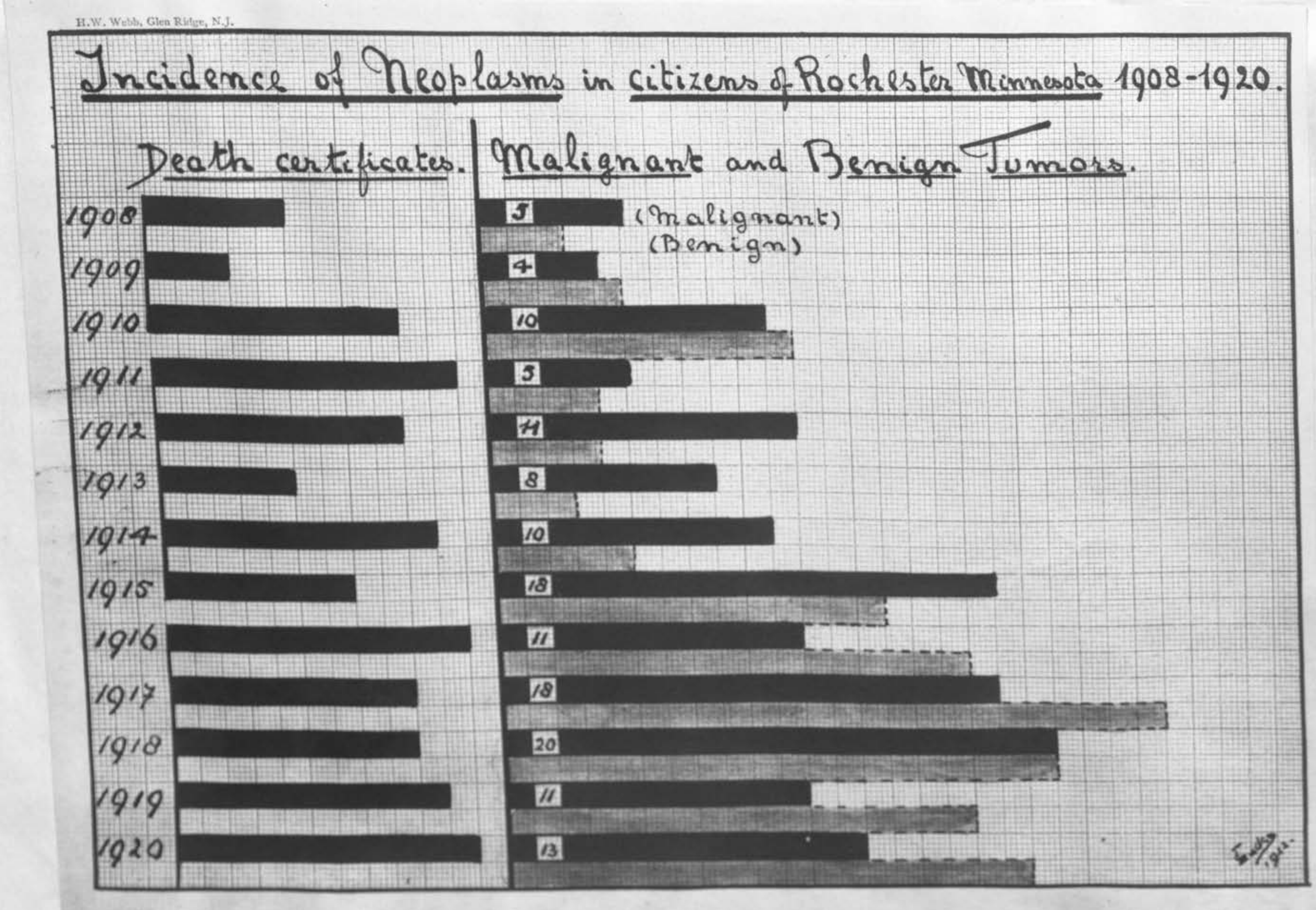

H.W. Webb, Glen Ridge, N.J.
Incidence of Neoplasms in citizens of Rochester Minnesota 1908-1920.
Death certificates.
Malignant and Benign Tumors.
(Malignant)
(Benign)
1908
1909
1910
1911
1912
1913
1914
1915
1916
1917
1918
1919
1920
5
4
10
5
11
8
10
18
11
18
20
11
13

Fig. 54.

H.W. Webb, Glen Ridge, N.J.

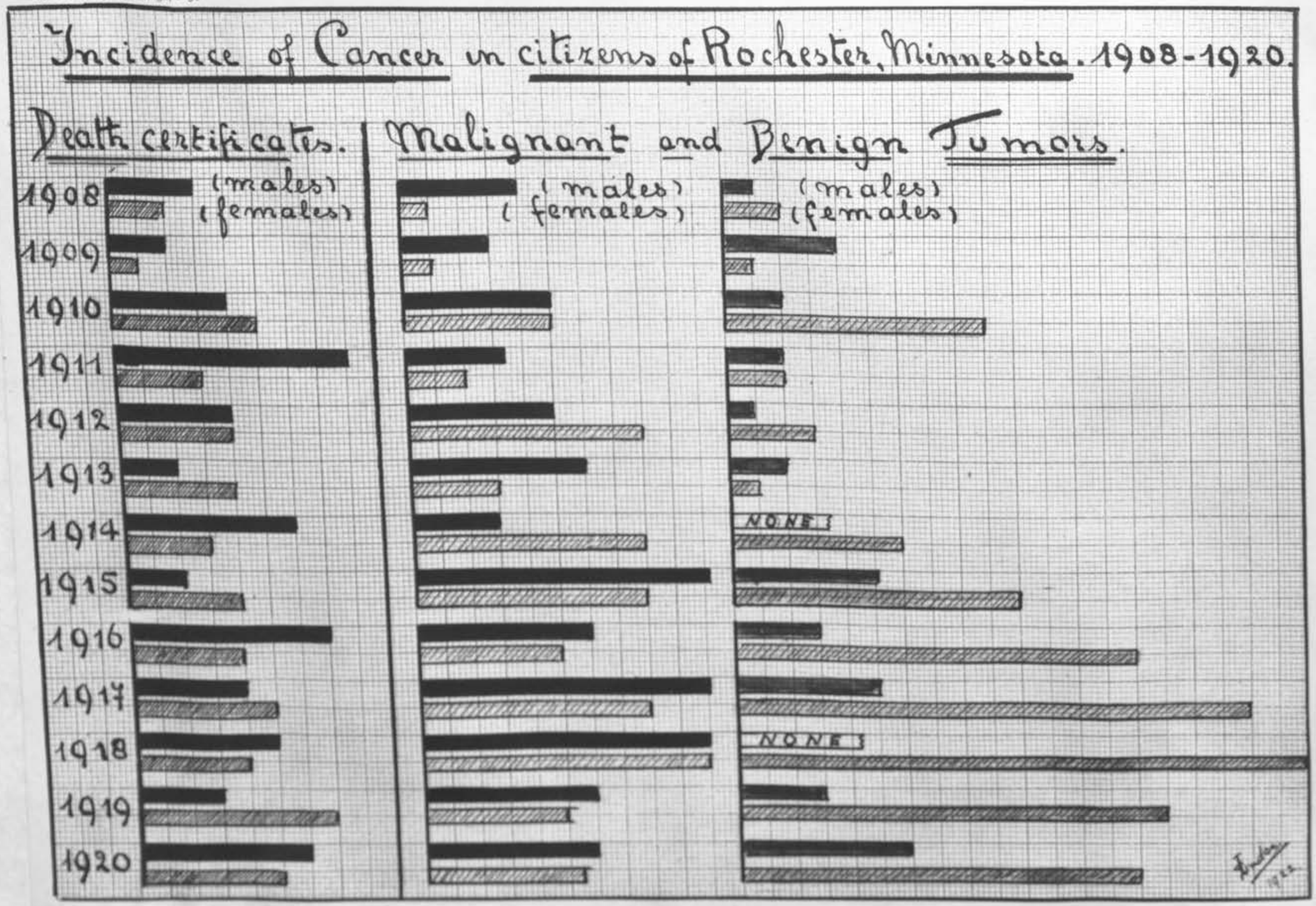


Fig. 55.

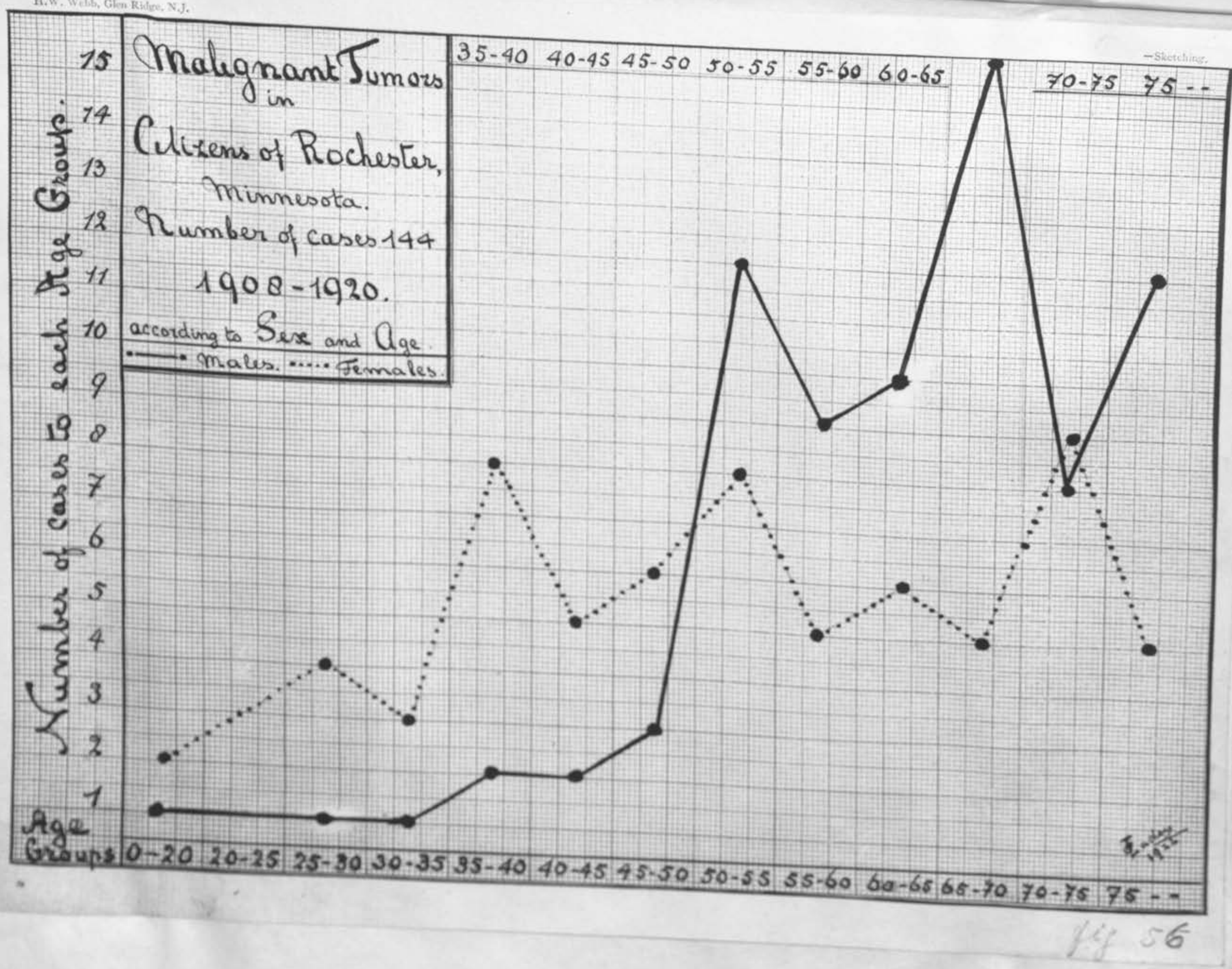
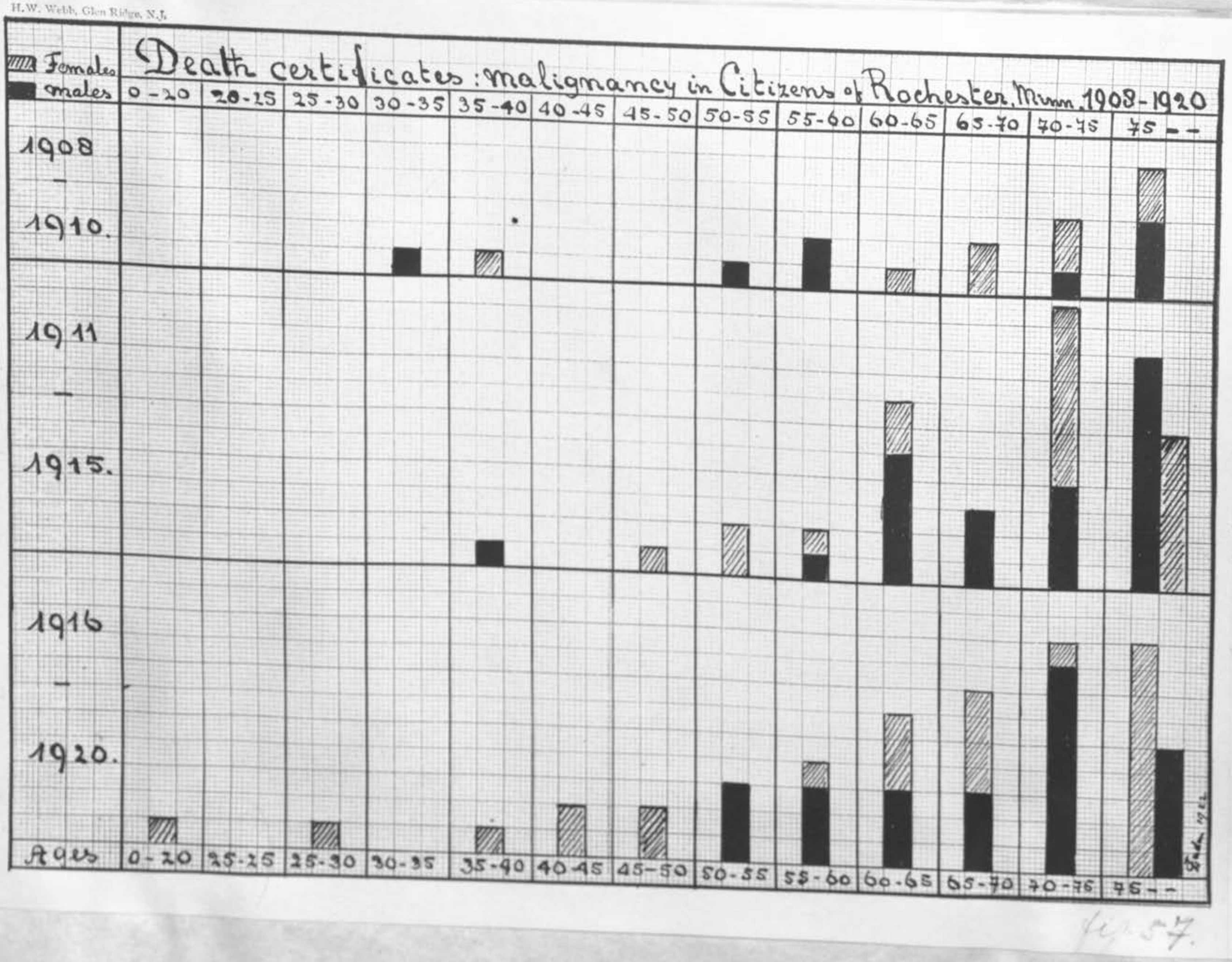

H.W. Webb, Glen Ridge, N.J.
-Sketching.
Malignant Tumors in Citizens of Rochester, Minnesota.
Number of cases 144
1908-1920.
according to Sex and Age.
Males. ..... Females.
Number of cases to each Age Group.
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
Age Groups
0-20 20-25 25-30 30-35 35-40 40-45 45-50 50-55 55-60 60-65 65-70 70-75 75 --
35-40 40-45 45-50 50-55 55-60 60-65 70-75 75 --
fig 56

Fig. 56.



H.W. Webb, Glen Ridge, N.J.
Death certificates: malignancy in Citizens of Rochester, Minn. 1908-1920
Females
males
0-20
20-25
25-30
30-35
35-40
40-45
45-50
50-55
55-60
60-65
65-70
70-75
75 - -
1908
1910.
1911
1915.
1916
1920.
Ages
fig 57.

FIG. 57.

H.W. Webb, Glen Ridge, N.J.

58

Fig. 58.

H.W. Webb, Glen Ridge, N.J.

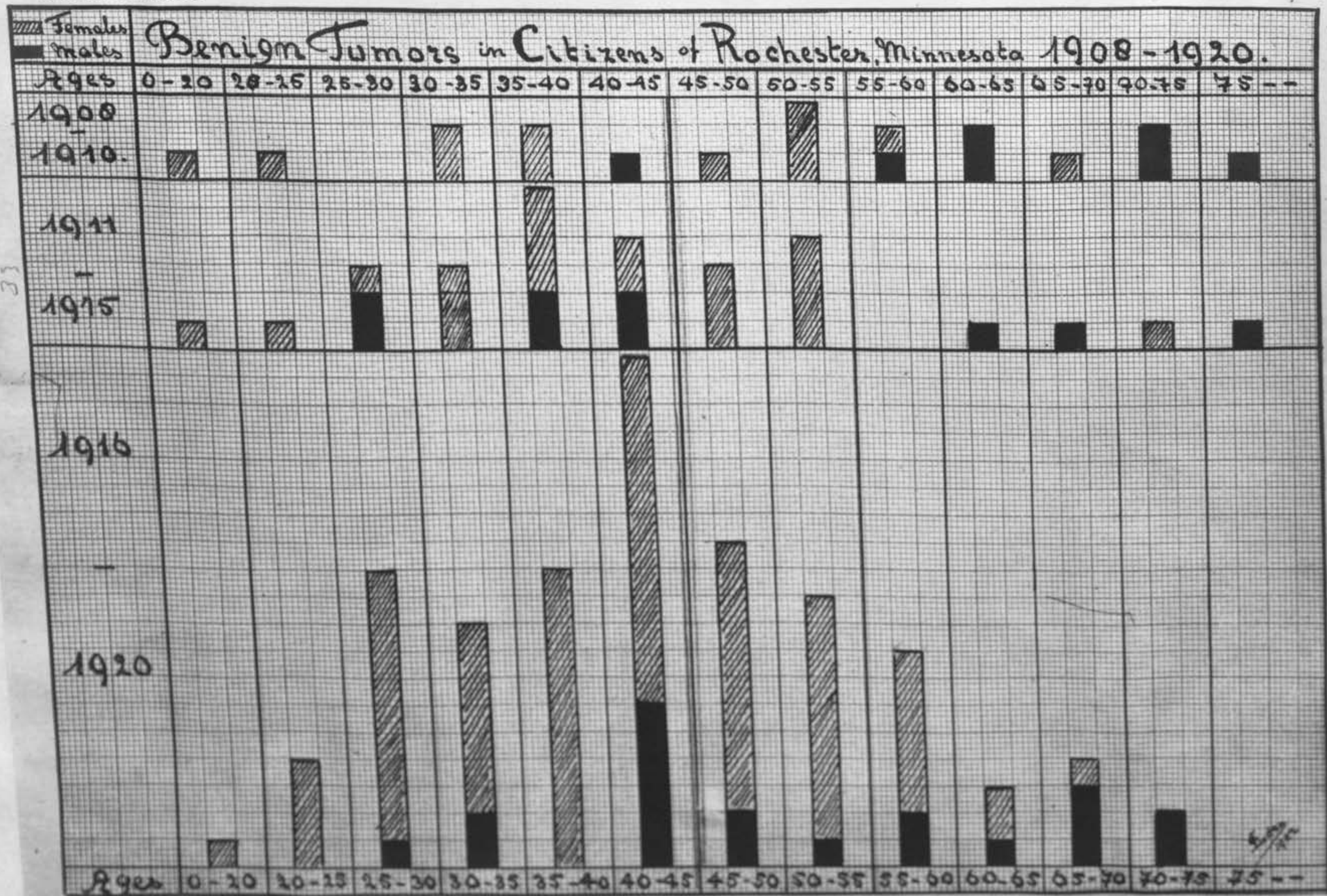


Fig. 59.

Fig. 60. City plan of Rochester, Minnesota, showing distribution and increase of large, smoke-producing buildings. Buildings erected before 1914 marked in outline only; buildings erected from 1914 to 1918 in solid black; buildings from 1918 to 1920 in hatched bars; buildings begun in 1920 "dotted". Observe that the buildings erected from 1914 to 1918 form a kind of barrier in the central, eastern portion of the city. The buildings erected after 1918 add to the width of this barrier and also form a second barrier running from East to West in the central southern portion of the city. The elimination of combustion products by the prevailing Northwest winds is thus impeded; their retention in the "cup" containing the main portion of the city is promoted.

Fig. 61 - a and b. Topography of Rochester, Minnesota: photographs showing uneven distribution of large and small buildings. The resulting uneven roof line promotes the formation of downdraughts and air-pockets and thus impedes the elimination of combustion products.

66

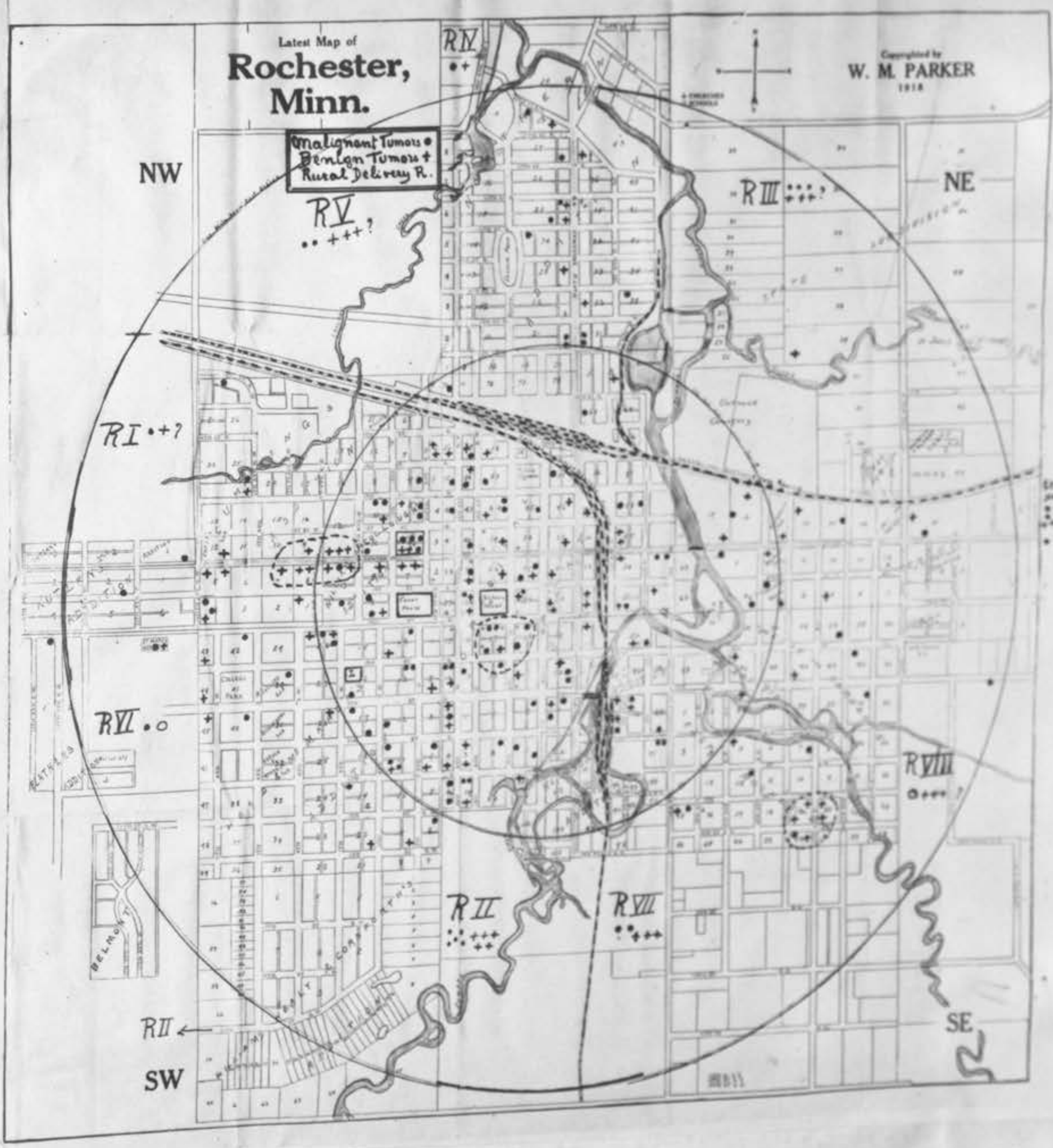


Fig. 62. City plan of Rochester, Minnesota, showing the distribution and location of the residences of citizens treated for malignant and for benign tumors at the Mayo Clinic from 1908 to 1920. Note the preponderance of both malignant and benign tumors in the central portion of the city, which is not the most densely populated part, but is situated at the bottom of the cup formed by the surrounding hills. Observe the frequent occurrence of benign and malignant tumors in the same city blocks. Malignant tumors (.); benign tumors(+); cases in which "rural delivery" is the only address available are given under R followed by Roman numeral; tumors appear to be more numerous in the rural districts R II and R VII, where the country is more hilly.

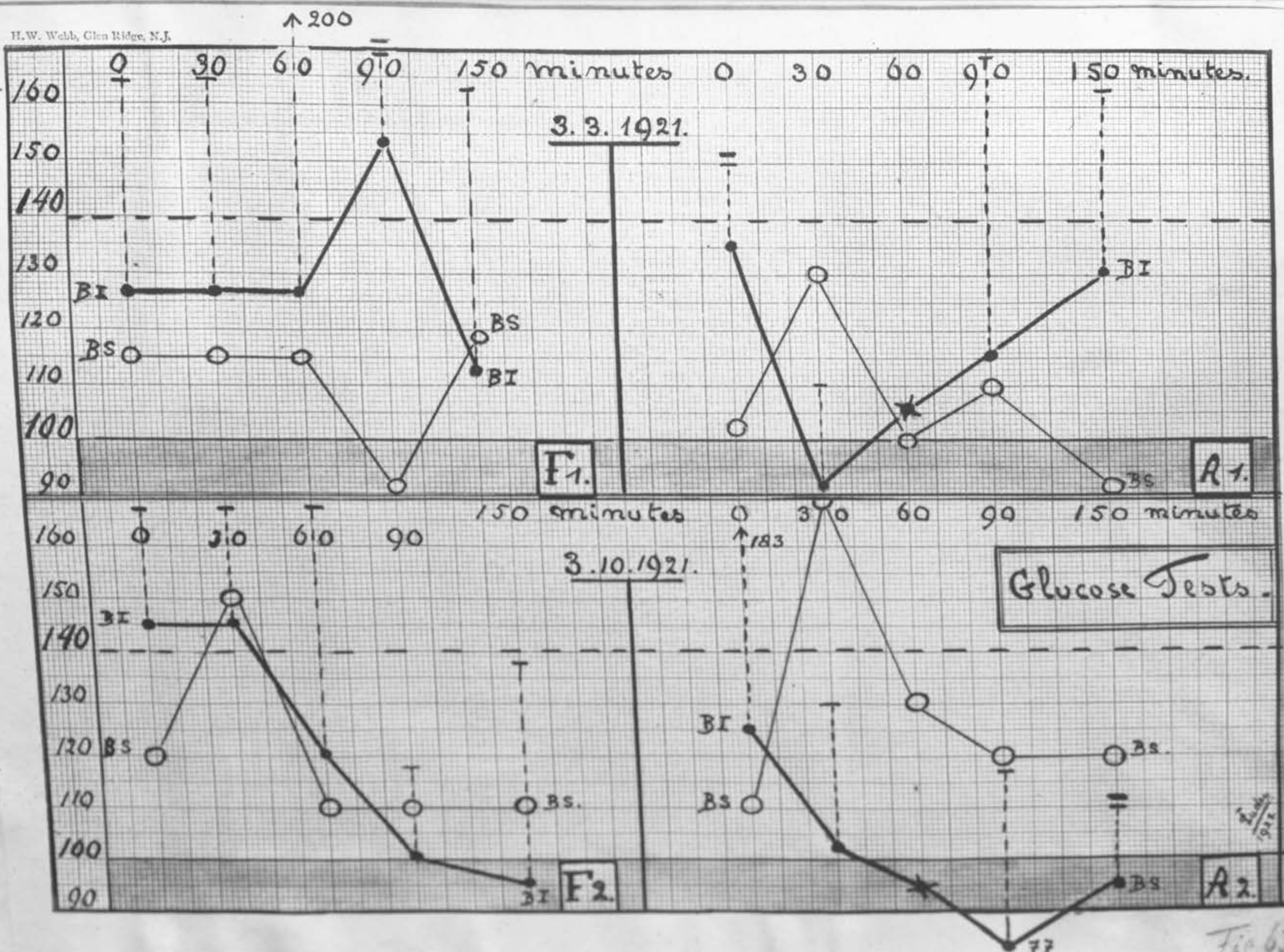

H. W. Webb, Glen Ridge, N.J.
Glucose Tests.
3. 3. 1921.
3. 10. 1921.
F1.
A1.
F2.
A2.
0
30
60
90
150 minutes
↑200
↑183
77
BI
BS
160
150
140
130
120
110
100
90

Fig. 63.

Fig. 63.

Legends

Fig. Topography of Rochester, Minnesota, showing location at the bottom of a "cup" formed by the surrounding hills; this "cup" contains the main portion of the city, including the business district.

Fig. 48. Topography of Rochester, Minnesota, showing uneven distribution of large and small buildings with resulting irregular roof line.

Fig. 50. Diagram of the incidence of cancer in citizens of Rochester, Minnesota, 1907-1918 (September). Analysis according to age; group of ninety citizens treated for malignancy at the Mayo Clinic. Microscopic diagnosis in sixty of the ninety cases.

Fig. 51. Diagram of the incidence of cancer in citizens of Rochester, Minnesota, 1907-1918 (September), showing relation of sex to age in five-year groups, for the entire group of ninety citizens; forty-five men and forty-five women.

Fig. 52. Diagram of the incidence of cancer in citizens of Rochester, Minnesota, 1907-1918 (September), showing the number of citizens each year during the eleven year period. Note the increasing incidence which is not explained by the two-fold increase of the resident population 1910-1920.

Fig. 53. City plan of Rochester, Minnesota, showing location of the residences of citizens treated for malignant conditions at the Mayo Clinic, 1907-1918 (September). Note the preponderance of malignancy in the center of the city, the smoke area, which is not the most thickly populated portion of the town. Malignant cases (.); benign cases (+); cases in which "rural delivery" was the only address (+?).

Fig. 54. Diagram of revised statistics of mortality and morbidity from malignant and benign tumors in citizens of Rochester, Minnesota, 1908-1920. Note the increasing incidence; the apparent decrease in 1919 and 1920 may be explained by an increased mortality from influenza during the epidemics in these

two years.

Fig. 55. Diagram of revised statistics of mortality and morbidity from malignant and benign tumors among citizens of Rochester, Minnesota, 1908-1920. Analysis according to sex: males, solid bars; females, hatched bars.

Fig. 56. Diagram of the incidence of malignant tumors in citizens of Rochester, Minnesota, 1908-1920, showing relation of sex to age in five-year groups. Note the earlier appearance in the females (dotted line) and numerical preponderance of males in the year groups having the highest incidence. Males, solid line; females, dotted line.

Fig. 57. Diagram showing analysis of death certificates for malignant disease in citizens of Rochester, Minnesota, 1908-1920 according to three periods: 1908-1910, 1911-1915, and 1915-1920, and according to age in five-year groups. Note the numerical increase with preponderance of the males in the second period in the later decades and the tendency to earlier development of malignancy, in which the females lead during the third period.

Fig. 58. Diagram showing analysis of the incidence of malignant tumors in citizens of Rochester, Minnesota, 1908-1920, as in Figure 56, according to periods and age groups. Note predominance of males in later decades of life and tendency to earlier development during the third period.

Fig. 59. Diagram showing analysis of the incidence of benign tumors in citizens of Rochester, Minnesota, 1908-1920, as in Figures 56 and 57, according to periods and age groups. Note predominance of females throughout, but increase among males and general tendency to earlier development in the third period.

Fig. 63. Diagrams of changes in the blood sugar and blood cholesterol values of A and F during glucose tolerance tests. March 3, 1921: ingestion of 100 gm. of impure, liquid glucose; March 7, 1921: ingestion of 100 gm. pure, powdered glucose. Note the reduction of split cholesterol (vertical broken line) in F 1 and 2, ninety minutes after ingestion of the glucose and the total

absence of split cholesterol in A 1 and 2, sixty minutes after. Compare with Figure 23 (oatmeal diet) and with Figure 45 (double adrenalectomised dogs); the findings suggest an interrelation between adrenals and pancreas, as the absence of suprarenals and increased pancreatic activity both appear to inhibit the production of split cholesterol. Discussed in Chapter XXI.